Nos. 15-2029, -2030, -2032

United States Court of Appeals for the Federal Circuit

PURDUE PHARMA L.P.,

Appellant,

v.

DEPOMED, INC.,

Appellee.

Appeal from the Patent Trial and Appeal Board in
IPR2014-00377, -00378, and -00379

BRIEF OF APPELLANT PURDUE PHARMA L.P.

SASHA MAYERGOYZ
JONES DAY
77 West Wacker
Chicago, IL 60601
(312) 269-1572
smayergoyz@
jonesday.com

JOHN J. NORMILE
GASPER J. LAROSA
LISAMARIE LOGIUDICE
JONES DAY
222 East 41st Street
New York, NY 10017
(212) 326-3939
jjnormile@jonesday.com
gjlarosa@jonesday.com
llogiudice@jonesday.com

GREGORY A. CASTANIAS
JENNIFER L. SWIZE
JONES DAY
51 Louisiana Avenue NW
Washington, D.C. 20001
(202) 879-3939
gcastanias@jonesday.com
jswize@jonesday.com

Counsel for Appellant Purdue Pharma L.P.

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for Appellant Purdue Pharma L.P. certifies as follows:

1. The full name of every party represented by me in this case is:

Purdue Pharma L.P.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

Jones Day: Gregory A. Castanias, Gasper J. LaRosa, Lisamarie LoGiudice, Sasha Mayergoyz, Lynda Q. Nguyen (no longer with firm), Kelsey I. Nix, John J. Normile, Jennifer L. Swize.

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TABLE OF ABBREVIATIONS

The following abbreviations are used in this brief.

Abbreviation	Term
377 Proceeding	*Inter Partes* Review Proceeding 2014-00377
378 Proceeding	*Inter Partes* Review Proceeding 2014-00378
379 Proceeding	*Inter Partes* Review Proceeding 2014-00379
’125 patent	U.S. Patent No. 5,945,125, titled “Controlled Release Tablet” (377 Proceeding—Ex. 1052; 378 Proceeding—Ex. 1056; 379 Proceeding—Ex. 1015)
’280 patent	U.S. Patent No. 6,635,280, titled “Extending The Duration Of Drug Release Within The Stomach During Fed Mode,” issued to Shell *et al*. (377 Proceeding—Ex. 1001)
’475 patent	U.S. Patent No. 6,340,475, titled “Extending The Duration Of Drug Release Within The Stomach During Fed Mode,” issued to Shell *et al*. (377 Proceeding—Ex. 1006; 378 Proceeding—Ex. 1001; 379 Proceeding—Ex. 1001)
’548 patent	U.S. Patent No. 4,871,548, titled “Controlled Release Dosage Form Comprising Different Cellulose Ethers” (377 Proceeding—Ex. 1017; 378 Proceeding—Ex. 1011; 379 Proceeding—Ex. 1032)
’837 patent	U.S. Patent No. 5,582,837, titled “Alkyl-substituted Cellulose-based Sustained-Release Oral Drug Dosage Forms” (377 Proceeding—Ex. 1010; 378 Proceeding—Ex. 1010; 379 Proceeding—Ex. 1006)

Baveja	S.K. Baveja *et al.*, "Zero-order release hydrophilic matrix tablets of β-adrenergic blockers" *International Journal of Pharmaceutics*, 39 (1987) 39-45 (377 Proceeding—Ex. 1008; 378 Proceeding—Ex. 1005; 379 Proceeding—Ex. 1013)
Colombo	P. Colombo *et al.* "Drug release modulation by physical restrictions of matrix swelling" *International Journal of Pharmaceutics*, 63 (1990) 43-4 (377 Proceeding—Ex. 1009; 378 Proceeding—1006; 379 Proceeding—Ex. 1014)
Kim	C.J. Kim, "Drug release from compressed hydrophilic POLYOX-WSR tablets" *Journal of Pharmaceutical Sciences*, 84 (3) (1995) 303-306 (377 Proceeding—Ex. 1019; 378 Proceeding—Ex. 1012; 379 Proceeding—Ex. 1047)
Board *or* PTAB	Patent Trial and Appeal Board
Depomed	Depomed, Inc.
Purdue	Purdue Pharma L.P.
AH	Alprenolol hydrochloride
HPMC	Hydroxypropylmethylcellulose
IPR	*Inter partes* review
MT	Metorprolol tartrate
POSITA	Person of Ordinary Skill in the Art

All emphasis is added throughout unless otherwise indicated.

STATEMENT OF RELATED CASES

The two patents-at-issue in this appeal, which arises from three related IPR proceedings, are involved in two patent-infringement suits pending before the U.S. District Court for the District of New Jersey: (1) *Depomed, Inc. v. Purdue Pharma L.P., et al.*, No. 13-00571-JAP-TJB (D.N.J.) ("*Depomed v. Purdue*"); and (2) *Depomed, Inc. v. Endo Pharmaceuticals Inc.*, No. 3:13-cv-02467-MLC-TJB (D.N.J.). On September 28, 2015, the district court entered an order staying *Depomed v. Purdue* pending this appeal.

The patents-at-issue are also involved in two other IPR proceedings, based on petitions filed by Endo Pharmaceuticals Inc.: *Endo Pharmaceuticals Inc., v. Depomed, Inc*., IPR2014-00654 and -00656 ("the *Endo* IPRs"). On September 21, 2015, the PTAB issued Final Written Decisions in the *Endo* IPRs, holding that the challenged claims were not proven to be unpatentable. At the time of filing of this opening brief, the period for noticing an appeal from the *Endo* IPR judgments has not yet run.

STATEMENT OF JURISDICTION

This appeal arises from three IPR proceedings initiated by Purdue before the PTAB pursuant to 35 U.S.C. §§ 311 et seq. to challenge the patentability of two Depomed patents. On July 8, 2015, the Board entered Final Written Decisions in the three proceedings, holding that Purdue had not established that the challenged claims of Depomed's patents were unpatentable. Purdue timely filed notices of appeal on August 3, 2015. (A1243-48; 35 U.S.C. § 142.) This Court, which consolidated the appeals on September 21, 2015, has jurisdiction under 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. §§ 141(c), 319.

STATEMENT OF THE ISSUES

Depomed's '475 and '280 patents—the two patents-at-issue—relate to controlled-release oral-dosage forms of a highly soluble pharmaceutical drug using a formulation that swells to promote retention in the stomach. The issue presented is:

Given the Board's findings that "each limitation of [the independent challenged] claim[s] was known in the art, as evidenced by the teachings of Baveja and the '837 patent," and that Baveja did "not teach away from the claimed invention," did the Board err in applying an overly restrictive standard for (a) analyzing whether a person of ordinary skill in the art (POSITA) would have

combined the prior-art references and (b) determining whether a POSITA would have had a reasonable expectation of success in making that combination?

STATEMENT OF THE CASE

A. Preliminary Statement

Unlike most obviousness cases, this appeal does not require ascertaining the scope of the prior art, determining the differences between the prior art and the claims, defining a POSITA's skill level, or construing the claims—all of those issues were correctly resolved by the Board. Rather, this appeal presents the narrow and specific question of whether a POSITA would have been motivated to combine two references with a reasonable expectation of success. And it is clear that a POSITA would have combined the two references—they relate to the same field, and already solved the problem of the claimed invention by teaching oral-dosage forms comprising the same types of polymers and drugs, and having overlapping drug-to-polymer weight ratios.

The Depomed patents-at-issue relate to orally administered, controlled-release dosage forms that swell to facilitate retention in the stomach in the presence of food ("during the fed mode"), and remain substantially intact in the stomach until all of the drug has been released. Gastric retention prolongs the time of controlled release into the stomach of drugs that are preferentially absorbed in the stomach or the upper gastrointestinal tract. Since the 1960s, scientists working on

formulating dosage forms have used the swellable polymers described in the '475 and '280 patents to control the release of high-solubility drugs.[1] Moreover, it was well-known that administering oral-dosage forms in the presence of food facilitates retaining the dosage form in the stomach.

The Board correctly found that all of the limitations of the challenged claims were present in the prior art. In particular, the Board found that the two primary references—the '837 patent (another Depomed patent from one of the same named inventors as on the patents-at-issue) and Baveja (a scientific journal article)—disclose all the limitations of the independent claims and most (or all) of the limitations of the dependent claims. The Board further found that three other references—the Colombo reference, the Kim reference, and the '125 patent—disclose the remaining limitations of the dependent claims. The Board correctly rejected Depomed's assertion that Baveja taught away from the claimed combinations. In addition, the Board properly construed the claims and correctly defined the POSITA as a highly skilled artisan having a Ph.D. in pharmaceutical science and industry experience developing controlled-release oral-dosage forms.

[1] A polymer is a substance having a molecular structure consisting of a large number of repeating units bonded together. In the context of the challenged claims, the polymer permits the dosage form to swell and thus controls the release of drug from the dosage form.

Despite all of that, the Board held that the claims were not obvious, ostensibly because Purdue failed to show "how or why" a POSITA would have combined the references to solve the problem purportedly addressed by the '475 and '280 patents. But the problem addressed by those patents—formulating oral-dosage forms that swell to facilitate retention in the stomach during the fed mode and remain substantially intact—was not a new one. The prior art not only identified the problem, but also taught the solution. In fact, Depomed's own prior-art '837 patent identified the problem and solved it using the same class of polymers, the same types of drugs, and overlapping drug-to-polymer weight ratios as claimed in the '475 and '280 patents. And Baveja confirmed that a specific combination disclosed in the '837 patent, and claimed in the '475 and '280 patents, successfully solved that problem. The '475 and '280 patents did no more than collect the prior-art teachings in their claims.

This is precisely the type of case for which the Supreme Court has given specific "instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007). *KSR* directs that "in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 420. Here, the teachings of the '837 patent and Baveja fit hand-in-glove, so that the "interrelated teachings of multiple [references]" themselves

provide the motivation to combine. *Id.* at 418. The Board committed legal error by failing to follow that standard and looking past the closely interrelated teachings of the prior art that had already solved the problem purportedly addressed for the first time in the patents-at-issue.

The Board likewise applied the wrong standard—and relied on legally irrelevant evidence—in evaluating a reasonable expectation of success. The '837 patent had already taught dosage forms that would swell and maintain their physical integrity in the stomach, and Baveja taught the successful manufacture and testing of dosage forms comprising the same types of polymer and drugs, and with overlapping drug-to-polymer ratios, as disclosed in the '837 patent. A POSITA thus would have "had every motivation to seek and every reasonable expectation of success in achieving" the dosage forms in the challenged claims. *In re Kubin*, 561 F.3d 1351, 1361 (Fed. Cir. 2009). The Board's reliance on inventor Helm's testimony that it took her years to develop the claimed inventions was legally irrelevant given Helm's admitted lack of knowledge of the prior art: the hypothetical POSITA knows all of the prior art. The Board's reliance on statements by Depomed's expert Dr. Hopfenberg regarding the number of possible formulation considerations was similarly inappropriate: His statements did not address or relate to the specific teachings of Baveja and the '837 patent, which clearly identified the critical parameters and even demonstrated actual success.

B. The Challenged Patents And Claims

The '475 and '280 patents are both titled "Extending The Duration Of Drug Release Within The Stomach During The Fed Mode." (A109-33; A134-57.)[2] They have identical specifications and name the same inventors—John Shell, Jenny Louie-Helm, and Micheline Markey.

The challenged claims of both patents recite oral-dosage forms comprising three elements: (1) a polymer matrix having swellable polymers such as hydroxypropylmethylcellulose ("HPMC"); (2) high-solubility drugs or drugs having at least one ionized group in the pH range 5 through 8; and (3) a particular drug-to-polymer weight-ratio range.[3] The patents claim that, with this formulation, the dosage forms will be retained in the stomach. (A109; A121:5:32-36; A134.) The remaining limitations recite performance characteristics of the dosage form, *e.g.*, "swelling," "dissolution and diffusion" or "erosion or diffusion," "remain[ing] substantially intact," and "releasing substantially all of said drug within [the] stomach."

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[2] The same exhibits were often submitted in multiple IPRs, and discovery in all three proceedings was conducted concurrently. For simplicity, this brief cites to exhibits from the 377 Proceeding, unless otherwise necessary.

[3] High-solubility drugs, in the context of the challenged claims, refer to drugs wherein less than ten parts water is required to dissolve one part drug. A drug has at least one ionized group in the pH range 5 through 8 because of the presence of amino or carboxyl groups in the drug molecule that are ionized (protonated or deprotonated) in aqueous media in that pH range.

1. The ’475 Patent

The ’475 patent was filed on March 29, 1999, and issued on January 22, 2002. Its challenged claims were addressed in two IPRs: (1) product claims 1, 8-10, 13-15, and 61-62 were the subject of the 378 Proceeding, and (2) method claims 43, 54-55, 57-58, and 66 were the subject of the 379 Proceeding. Claims 1 and 43 were the challenged independent claims. Claim 1 and its dependent claims have a priority date of June 6, 1997. Claim 43 and its dependent claims have a priority date no earlier than March 29, 1999.

Claim 1, which is representative of the product claims, is reproduced below with shorthand references for each limitation provided in brackets:

> 1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water [“solubility limitation”],
>
> said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20 [“weight ratio limitation”],
>
> said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode [“swelling limitation”],
>
> that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid [“dissolution and diffusion limitation”],
>
> that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion [“retains at least about 40% limitation”]

and releases substantially all of said drug within about eight hours after such immersion ["releases substantially all limitation"],

and that remains substantially intact until all of said drug is released ["substantially intact limitation"].

(A152:17:45-59.)

The challenged claims that depend from claim 1 recite specific aspects of the claimed dosage form, such as the type of polymer (including alkyl-substituted celluloses such as HPMC (claims 8-10, 57-58, and 61-62)), the amount of drug retained one hour after immersion in gastric fluid (claims 13-15), and the polymer's molecular weight (claims 57-58).

Independent method claim 43 recites:

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8 ["ionized group limitation"],

said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode ["administration in the fed mode limitation"],

said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20 ["weight ratio limitation"],

said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode ["swelling limitation"],

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion

> of said dissolved drug out of said matrix ["erosion or diffusion limitation"],
>
> (c) retains at least about 40% of said drug one-hour after such immersion in gastric fluid ["retains at least about 40% limitation"],
>
> (d) releases substantially all of said drug within about ten hours after such immersion, ["releases substantially all limitation"] and
>
> (e) remains substantially intact until all of said drug is released ["substantially intact limitation"],
>
> thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment ["releasing substantially all in the stomach limitation"].

(A156:25:39-64.)[4] Claim 66, which depends from claim 43, recites a specific polymer and viscosity. (A157:27:23-26.)

2. The '280 Patent

The '280 patent, filed on November 6, 2001, and issued on October 21, 2003, is a continuation of the application that issued as the '475 patent. Challenged claims 1, 8-10, 13-15, 43, and 45-46 of the '280 patent, which were the subject of the 377 Proceeding, are very similar to their counterparts in the '475 patent. Claims 1 and 43 were the challenged independent claims; they and their dependent claims have the same priority dates as their counterparts in the '475 patent.

[4] Although the individual limitations may differ among claims of the '475 and '280 patents, the claims share the same categories of limitations, as the shorthand brackets indicate.

Claim 1 of the ’280 patent recites:

> 1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water [“solubility limitation”],
>
> said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20 [“weight ratio limitation”],
>
> said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode [“swelling limitation”],
>
> that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid [“dissolution and diffusion limitation”],
>
> that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion [“retains at least about 40% limitation”]
>
> and releases substantially all of said drug after such immersion [“releases substantially all limitation”],
>
> and that remains substantially intact until substantially all of said drug is released [“substantially intact limitation”].

(A127:17:45-61.) All of the challenged dependent claims of the ’280 patent depend from claim 1. Similar to their counterparts in the ’475 patent, these dependent claims recite specific details such as the type of polymer (claims 8-10), the percentage of drug retained one hour after immersion in gastric fluid (claims 13-15), and duration by which substantially all of the drug is released (claims 45-46).

Claim 43 covers a method of administering a drug and recites the same limitations as claim 43 of the ’475 patent, except that it omits the “substantially intact” limitation. (A131:25:37-62.)

The minor differences between the challenged claims of the ’475 and ’280 patents are:

- Claim 1 of the ’475 patent requires that the dosage form “swell[] upon imbibition of water” to “a size large enough to promote retention in stomach during said fed mode,” whereas claim 1 of the ’280 patent requires that the dosage form “when swollen in a *dimensionally unrestricted manner* as a result of imbibition of water [gastric fluid in claim 43] is of a *size exceeding the pyloric diameter* in the fed mode to promote retention in the stomach during said fed mode.”
- Claim 1 of the ’475 patent requires that the dosage form “upon immersion in gastric fluid … releases substantially all of said drug *within about eight hours* after such immersion,” whereas claim 1 of the ’280 patent does not specify a time period.
- Claim 1 of the ’475 patent requires the dosage form to remain “substantially intact until *all* of said drug is released,” whereas claim 1 of the ’280 patent requires the dosage form to remain “substantially intact until *substantially all* of said drug is released.”

Due to their similarity, this brief addresses the independent claims of the ’475 and ’280 patents collectively.

C. Procedural History

Purdue filed three IPR petitions on January 24, 2014. In support of the proposed grounds for unpatentability, Purdue submitted the declaration of technical expert Professor Roland Bodmeier, Ph.D., who explained what the art would have conveyed to a POSITA at the time of the alleged inventions. (A1908-87.) As Dr. Bodmeier explained, the prior-art references that Purdue submitted to the Board disclosed oral-dosage forms comprising a polymer matrix with high-solubility drugs, at drug-to-polymer weight ratios that satisfy the limitations of the challenged claims. Purdue also submitted the declaration and report of technical expert Professor Kinam Park, Ph.D., who conducted tests on prior-art formulations to support Purdue’s grounds for unpatentability. (A2012-27; A2028-45.)

Based on largely overlapping grounds for relief and prior-art references, the Board instituted review in all three proceedings on July 10, 2014. Although the Board did not grant institution based on anticipation by the ’837 patent or Baveja as Purdue requested, the Board recognized that both were primary references for

obviousness.[5] When instituting the IPRs, the Board recognized that the nature of the problem to be solved provided a reason to combine the '837 patent and Baveja:

> [A POSITA] would have a reason to combine Baveja, the '837 patent, and the '548 patent given the nature of the problem to be solved: "to formulate a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." …. Thus, on this record, we are persuaded that Petitioner has shown sufficiently that one of ordinary skill in the art would have had a reason to combine the teachings of the references to reach the claimed invention.

(A340; A14700; A28809.)[6]

As relevant here, the Board instituted review on whether the challenged claims were obvious given the combination of the '837 patent and Baveja and, with respect to certain dependent claims, also in combination with Colombo, Kim, and the '125 patent.[7]

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[5] Purdue reserves the right to pursue elsewhere grounds of invalidity or unpatentability on which the Board did not institute.

[6] Given the Board's finding in its Final Written Decisions that the '548 patent did not teach certain limitations, the Board "d[id] not address further the proposed combination[s]" involving that reference. (A24; A61.) This appeal likewise does not address the '548 patent.

[7] Specifically, for certain dependent claims, the Board instituted review on the following grounds: whether claim 10 of each patent would have been obvious given the combination of Baveja, Kim, and the '837 patent; whether claims 8-9, 13-14, and 61-62 of the '475 patent would have been obvious given the combination of the '837 patent and Colombo; whether claims 57-58 and 66 of the '475 patent would have been obvious given the combination of the '837 patent, Baveja, and Colombo; and whether claims 54 and 55 of the '475 patent would have

D. The Prior Art

The Board found "that each limitation of [the independent] claim[s] was known in the art, as evidenced by the teachings of Baveja and the '837 patent." (A23; A60; A98.) The Board also found that Colombo, Kim, and the '125 patent, along with Baveja and the '837 patent, disclose various limitations of the dependent claims. (A31-32; A105.)

1. The '837 Patent

The '837 patent, titled "Alkyl-substituted Cellulose-based Sustained-Release Oral Drug Dosage Forms," issued on December 10, 1996 (and is now expired).[8] (A13-14; A54.) Like the '475 and '280 patents, the '837 patent is assigned to Depomed and lists John Shell—the lead inventor of the '475 and '280 patents—as the sole inventor.

Like the '475 and '280 patents, the '837 patent is directed to a controlled-release oral-dosage form that swells in a dimensionally unrestricted manner to promote gastric retention of the dosage form in the fed mode, and that maintains its physical integrity over the dosing period. (A1820:1:58-2:10; A1822:5:9-12;

(continued…)

been obvious given the combination of the '837 patent, Baveja, Colombo, and the '125 patent.

[8] The terms "controlled release" and "sustained release" describe a mechanism of releasing a drug from a dosage form more slowly compared to immediate release of the drug. For this appeal, the terms are used interchangeably.

A1826:13:56-14:15; A1929 ¶ 48.) In its "Summary of the Invention," the '837 patent states that "[t]he invention is a *sustained-release oral drug dosage form* for releasing a solution of a drug into the stomach…that (i) *swells unrestricted dimensionally* … to *promote gastric retention of the pellets in fed-mode* induced patients… (ii) permits *dissolution* of the dispersed drug by imbibed gastric fluid … and release of the resulting solution… and (iv) *maintains its physical integrity* over at least a substantial portion of the time period during which the drug is released into the stomach." (A1820:1:58-2:10; A1936 ¶ 65; A1958 ¶ 126; A1980-81 ¶¶ 180-82.) The Board expressly found that the '837 patent discloses the "swelling" and "substantially intact" limitations, and its Final Written Decisions demonstrate that the other limitations of the independent claims are also disclosed, except for the "releases substantially all" limitation because Figure 1 only depicts release up to seven hours, at which point less than substantially all of the drug had been released. (A17-18; A22-26.)

As Purdue's expert Dr. Bodmeier explained, to appreciate just how closely the '837 patent is tied to the other prior art (discussed in detail below), one need only look at the disclosures of the '837 patent itself. For instance, to formulate oral-dosage forms, the '837 patent teaches a class of polymers that include cellulose-based swellable polymers and identifies HPMC as one example. (A1825:11:39-43; A1826:13:59-64; A1827:16:25-26; A1962 ¶ 133.) Likewise, the

'837 patent discloses that the oral-dosage form includes a drug having a "solubility … in the range of 0.01% to about 35% by weight." (A1820:2:35-37; A1959 ¶ 128.) The '837 also provides examples of high-solubility drugs, such as diltiazem (A1821:4:10; A1825:12:22) and captopril (A1821:3:37.) The '837 patent further teaches that the "weight ratio of drug to polymer in the mixture or dispersion will normally be 1:9 to 9:1." (A1822:5:2-6; A1980 ¶ 174.) In addition, the '837 patent discloses drug-release profiles, directing that the drug should be released in not less than about two hours and teaches a range of release times such as an "8-14 hour duration." (A1825:12:20-25.)

2. Baveja

The Baveja reference, titled "Zero-Order Release Hydrophilic Matrix Tablets of β-Adrenergic Blockers," was published in 1987 by S.K. Baveja *et al*. in the *International Journal of Pharmaceutics*. (A1804-10.) The hydrophilic matrix tablets disclosed in Baveja swell upon ingress of water. (A1804; A1692-93:8:15-9:5.) The Board found that, except for the "swelling" and "substantially intact" limitations, Baveja expressly teaches every limitation of the independent claims—including the "releases substantially all" limitation. (A20-21; A56-57; A94-95.)

Like the '837 patent, Baveja relates to the field of controlled-release oral-dosage forms comprising swellable polymeric matrices containing an alkyl-substituted cellulose and drug. (A1804-05; A1952 ¶ 105.) As in the '837 patent,

Baveja's formulations use HPMC, and Baveja identifies the specific brand of HPMC used as Methocel K4M Premium. (A1805; A1940 ¶ 75.) According to the patents-at-issue, the "water swellability of these polymers," including HPMC, "cause[s] the drug-containing matrices to swell in size…due to ingress of water in order to achieve a size that will be retained in the stomach…." (A123:9:1-5; A1692:9:1-4.)

As in the '837 patent, Baveja describes oral-dosage forms having high-solubility drugs, such as alprenolol hydrochloride (AH) or metoprolol tartrate (MT), both of which have solubilities within the range described in the '837 patent and claimed in the '475 and '280 patents. (A1804-10; A1940 ¶ 75; A1959 ¶ 128.) And Baveja actually made combinations falling within the '837 patent and the patents-at-issue, performing tests on them and recording various attributes relevant to the patents-at-issue.

In Figure 1, Baveja reports test results demonstrating the cumulative percent of AH released as a function of time, from tablets containing AH and HPMC in various drug-to-polymer ratios. (A1944 ¶¶ 85-86.) Baveja's Figure 2 provides the same test results for dosage forms having various drug-to-polymer ratios of MT and HPMC. (A1944 ¶¶ 85-86.)

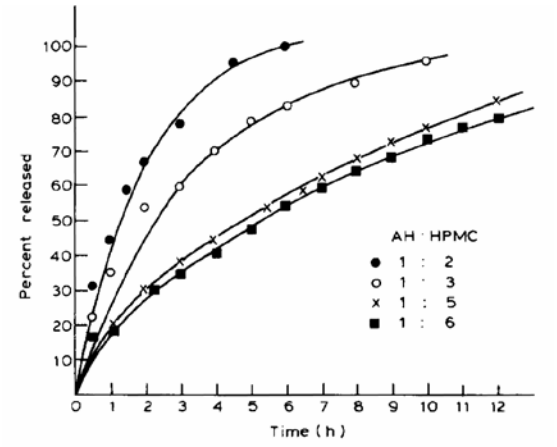

Fig. 1

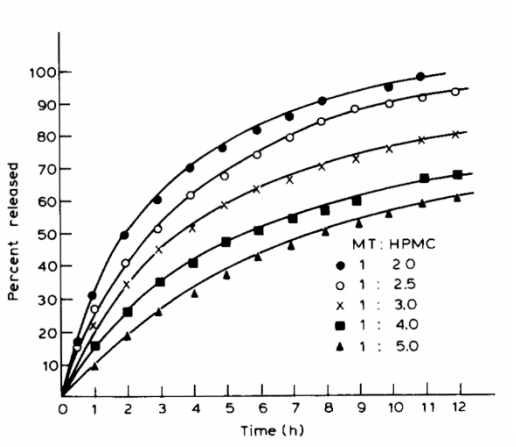

Fig. 2

The dosage forms shown in Figures 1 and 2 have drug-to-polymer weight ratios within the range described in the ’837 patent and claimed in the ’475 and ’280 patents. (A1940 ¶ 76; A1958 ¶ 127.) Moreover, as shown by the solid circles in Figure 1, Baveja teaches a dosage form comprising AH and HPMC with a 1:2 drug-to-polymer ratio, that will retain at least 40% of the drug one hour after immersion in gastric fluid and release substantially all of the drug (*i.e.*, at least 80%) within three hours. (A1806, Fig. 1; A1944 ¶¶ 85-86.) Accordingly, Baveja supplies the specific drug kinetic properties that the Board thought were absent from the ’837 patent, and does so in a way that is plainly complementary to the teachings of that patent.

3. Colombo

The Colombo reference, titled “Drug Release Modulation By Physical Restrictions of Matrix Swelling,” was published in 1990 by P. Colombo *et al.* in the *International Journal of Pharmaceutics*. (A1811-16.)

Colombo relates to the field of controlled-release oral-dosage forms comprising swellable polymeric matrices containing an alkyl-substituted cellulose and a highly soluble drug. As with the '837 patent and Baveja, Colombo's dosage forms are formulated with HPMC. (A1947 ¶ 90.) Colombo identifies the use of HPMC (Methocel K100 M) having a viscosity of about 100,000 centipoise, which falls within the claimed viscosity range recited in dependent claims 62 and 66 of the '475 patent. (A1812; A15647 ¶ 110; A30147-48 ¶ 110.) Colombo also teaches oral-dosage forms having drug-to-polymer ratios within the range of the '837 patent. (A1812; A1966 ¶ 144.) Moreover, as in the '837 patent and Baveja, Colombo's oral-dosage forms control the release of the high-solubility drug diltiazem. (A1812; A1947 ¶ 90; A1966 ¶ 145.)

4. The Kim Reference And The '125 Patent

The **Kim reference**, titled "Drug Release From Compressed Hydrophilic POLYOX-WSR Tablets," was published in 1995 by Kim *et al*. in the *Journal of Pharmaceutical Sciences*. (A2008-11.) Kim teaches oral-dosage forms that control the release of the high-solubility drug diltiazem—disclosed in the '837 patent, which is dispersed in a matrix comprising high-molecular-weight poly(ethylene oxide) (PEO) (another water-soluble polymer). (A2008; A1972 ¶ 160.) Kim teaches that both PEO and HPMC are "good candidate[s] for oral drug delivery systems." (A2010; A1972 ¶ 160.) Kim also discloses that others

"observed similar release kinetics with PEO and HPMC." (A2009; A1972 ¶ 160.) The Board found that Kim teaches the limitation of claim 10 in the '475 and '280 patents, which requires a polymeric matrix formed of PEO at a molecular weight of at least about 4,000,000. (A32; A68.)

The **'125 patent**, titled "Controlled Release Tablet," issued on August 31, 1999, to C.J. Kim, author of the Kim reference. (A2507-47.) Like the '837 patent and Baveja, the '125 patent is directed to oral-dosage forms that control the release of a highly soluble drug dispersed in a matrix comprising a swellable polymer, including HPMC. (A30146 ¶ 106.) The '125 patent discloses that "[b]oth PEO and HPMC are useful alone. Alternatively, mixtures of the two materials … may be used in the present invention." (A2541:4:26-29.) The '125 patent teaches specific examples of formulations containing HPMC (A2523-24, Figs. 15, 16), and uses diltiazem as the model drug. (A2542:6:35-36; A30121 ¶ 46.) The Board found that the '125 patent "teaches a drug dosage form comprising a drug and PEO having a molecular weight of 5,000,000" (A105), satisfying the limitations recited in claims 54 and 55 of the '475 patent.

E. The Board's Decisions

A consolidated oral hearing for the proceedings was held on March 19, 2015, and the Board issued its Final Written Decisions on July 8, 2015, in which it construed various claim limitations. Given the overlap in claimed subject matter in

the ’475 and ’280 patents, and the common set of prior-art references used to challenge patentability, the Board’s Final Written Decisions in all three IPRs are very similar, and in many instances identical.

Addressing obviousness in all three Decisions, the Board found “that each limitation of [the challenged independent] claim[s] was known in the art,” and specifically pointed to “the teachings of Baveja and the ’837 patent.” (A23; A60; A98.) Rejecting Depomed’s argument, the Board found that Baveja “does not teach away from the claimed invention.” (A20; A57; A93-94.) The Board also defined a POSITA as highly skilled: “a person with a Ph.D. degree in at least pharmaceutical science, chemistry, or chemical engineering along with at least two years of industry experience in the development of controlled-release oral dosage forms” or “hav[ing] an equivalent level of skill through similar education, training, and industry experience.” (A15; A51-52; A85.)

However, the Board concluded that Purdue did not establish “that there was a reason to combine [the ’837 patent and Baveja] to achieve the claimed invention with a reasonable expectation of success.” (A23; A63; A98.) The Board stated that “[a]lthough the references may have interrelated teachings, as Petitioner asserts, Petitioner has not explained persuasively *how* or *why* a [POSITA] would have combined the ‘swelling’ and ‘substantially intact’ features of the ’837 patent formulation with the formulation of Baveja.” (A26; A63; A100-01 (original

emphasis).) The Board reached this conclusion without properly applying the rule that a reason to combine can be implicit from "look[ing] to interrelated teachings of multiple patents." *KSR*, 550 U.S. at 418. The Board also discounted the nature of the problem to be solved as providing the "*how* or *why*" of a reason to combine, summarily concluding that "Petitioner's recitation of the [] problem to be solved is essentially a recitation of [the challenged] claim[s]"—even though the Board itself adopted that definition of the problem in instituting the IPRs. (A27; A64; A102.) As shown below, the Board failed to consider that Purdue's definition of the problem to be solved was taken directly from the prior-art '837 patent, not from the challenged claims.

The Board also concluded that a POSITA would not "have had a reasonable expectation of success, in part, because both parties' declarants testified about the number of formulation considerations at play when preparing a drug formulation." (A29; A65; A103.) The Board reached this conclusion by citing testimony from various witnesses, but it ignored the fact that this testimony did not address the specific formulations and test results already taught in the '837 patent and Baveja. As shown below, Baveja not only demonstrates a reasonable expectation of success, it establishes actual success. The Board further relied on the testimony of inventor Helm as a representative POSITA, but Ms. Helm conceded that she was not aware of the prior-art references when working on the claimed inventions.

(A25-26; A62; A100.) Similarly, the Board relied on testimony by Depomed's expert Dr. Hopfenberg that failed to account for the specific teachings of the '837 patent and Baveja. (A:29; A9340-41 ¶ 59; A9390-91 ¶ 161.)

SUMMARY OF ARGUMENT

The challenged claims would have been obvious to a POSITA. The Board correctly found that a POSITA would have concluded that the prior art disclosed the polymer-drug combinations and the resulting performance characteristics recited in the challenged claims. Despite those findings, the Board held that Purdue failed to show "how or why" a POSITA would have been motivated to combine the '837 patent and Baveja. The Board reached this conclusion by deviating from *KSR*'s guidance that the obviousness analysis involves an "expansive and flexible" approach rather than application of formalistic rules. The obviousness analysis must account for the interrelated teachings of the prior art, a POSITA's common sense, and the nature of the problem to be solved. Applied here, those principles demonstrate "how" and "why" a POSITA would have combined the overlapping teachings of the '837 patent and Baveja to achieve the challenged claims. Indeed, the prior-art teachings already solved the problem the challenged claims purportedly solve. The Board looked past this fundamental fact because it erroneously attributed Purdue's definition of the problem as derived

from the challenged claims. Purdue's definition, however, comes directly from the prior-art '837 patent.

The Board also erroneously concluded that Purdue failed to show that a POSITA would have reasonably expected success from combining the two references. The teachings of the '837 patent and Baveja demonstrate actual success, far more than required under this Court's standard. Again, the Board looked past this evidence and instead relied on legally irrelevant testimony of inventor Helm, who admitted that she was not aware of the prior art and lacks the educational background of a POSITA. The Board's reliance on Dr. Hopfenberg's testimony was equally incorrect because it too was divorced from the explicit teachings of the '837 patent and Baveja.

The Board's rulings should be reversed.

STANDARDS OF REVIEW

This Court reviews "the Board's compliance with governing legal standards *de novo* and its underlying factual determinations for substantial evidence." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013). "[S]ubstantial evidence" requires "more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000). A determination regarding

obviousness is a legal question reviewed *de novo*, and the subsidiary factual findings are reviewed for substantial evidence. *Id.* at 1316.

ARGUMENT

"A patent may not be obtained if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1346 (Fed. Cir. 2009). Here, the Board correctly determined that "each limitation of [the challenged independent] claim[s] was known in the art, as evidenced by the teachings of Baveja and the '837 patent." (A23; A60; A98.) The Board further correctly found that a POSITA would have been highly skilled. (A15; A51; A85.) The Board also correctly found that Baveja did not "teach away from the claimed invention." (A20; A57; A94-95.)

The Board, however, applied the wrong legal standards when analyzing the motivation to combine, improperly requiring Purdue to produce evidence beyond establishing the "interrelated teachings" of the prior-art references. *KSR*, 550 U.S. at 418. As a result, the Board's erroneous decision "*was mainly the result of the analytical errors* ... not the Board's resolution of factual questions." *Smith & Nephew, Inc. v. Rea*, 721 F.3d 1371, 1380 (Fed. Cir. 2013) (reversing

determination of non-obviousness when Board made correct factual findings but committed legal errors in applying obviousness standard).

I. A POSITA WOULD HAVE BEEN MOTIVATED TO COMBINE THE '837 PATENT AND BAVEJA

"Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *KSR*, 550 U.S. at 419. *KSR* thus "reject[ed] the rigid approach" for combining teachings of related prior-art references, emphasizing instead the application of "an expansive and flexible approach." *Id.* at 415. Accordingly, an obviousness analysis must account for the "*interrelated teachings* of multiple patents [or other prior-art references]" and "*any need or problem known in the field* of endeavor at the time of invention," such that when "a technique has been used to improve one device, [] a person of ordinary skill in the art would recognize that it would improve similar devices in the same way." *Id.* at 417-20.

A. The Interrelated Teachings Of The '837 Patent And Baveja Provide The Reason To Combine The References

This Court "'ha[s] explained that the '[m]otivation to combine may be found in many different places and forms.'" *PAR Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014). A POSITA may find reason to combine references to achieve a claimed invention even absent an explicit mention in one reference of the other. *KSR*, 550 U.S. at 417; *Alza Corp. v. Mylan Labs., Inc.*, 464

F.3d 1286, 1291 (Fed. Cir. 2006) ("[A] motivation to combine may be found in *implicit* factors."). In fact, "*KSR* expanded the sources of information for a properly flexible obviousness inquiry to include … the *'interrelated teachings of multiple patents'*… and the background *knowledge, creativity, and common sense*" of a POSITA. *Perfect Web Techs., Inc. v. InfoUSA, Inc*., 587 F.3d 1324, 1329 (Fed. Cir. 2009).

Applied here, those sources establish that a POSITA, having a Ph.D. in pharmaceutical sciences and industry experience developing controlled-release oral-dosage forms (A15), would have had ample motivation to combine the complementary teachings of the '837 patent and Baveja to obtain the challenged independent claims and all (or most) of the limitations of the challenged dependent claims. Both the '837 patent and Baveja relate to the same field, address the same types of formulations, teach similar sustained-release profiles, and describe overlapping drug-to-polymer ratios as the '475 and '280 patents. (A1958 ¶¶ 127-30.)

Both References Pertain To The Same Field: The '837 patent and Baveja relate to the same narrow, specialized field of endeavor—formulation of controlled-release oral-dosage forms using hydrophilic, cellulose-based polymers. The '837 patent states that "[t]his invention … relates specifically to alkyl-substituted *cellulose-based sustained release drug dosage forms*." (A1820:1:17-

19.) Likewise, Baveja notes that "[h]ydrophilic matrix systems have attracted considerable attention in recent years as *sustained release devices* for delivery of water soluble drugs…. *Cellulose derivatives are the most commonly used for oral sustained-release tablet formulations*." (A1804.)

Both References Teach Formulations Comprising The Same Types of Polymers and Soluble Drugs: The '837 patent and Baveja disclose formulating sustained-release oral-dosage forms comprising the same swellable, cellulose-based polymers and soluble drugs. The '837 patent describes a class of swellable polymer—"alkyl-substituted cellulose that [ ] swell[] unrestricted dimensionally via imbibition of water from gastric fluid … to promote retention of the pellets in fed mode induced patients." (A1820:1:58-64; A1826:13:59-64; A1961-62 ¶ 132.) The '837 patent discloses and claims specific types of swellable polymers, including HPMC. (A1820:1:58-64; A1825:11:24-25; A1825:11:39-43; A1826:13:59-64; A1827:16:25-26; A1958 ¶ 127.)

The '837 patent also teaches a solubility range for drugs used in the dosage form: "Normally, the solubility of the drug (measured in water at 37° C) will be in the range of 0.01% to about 35% by weight, more normally 0.01% to 5% by weight" in order to "permit [the drug] to dissolve and leach from the particles at a rate that provides the effective level for therapy and the desired duration of treatment." (A1820:2:32-38; A1959 ¶ 128.) The '837 patent then identifies

examples of highly soluble drugs, such as captopril and diltiazem. (A1821:3:9-37; A1821:4:10; A1821:4:27; A1825:12:20-25; A1826:14:66-67; A1959 ¶ 128.)

Baveja describes the manufacturing and testing of oral-dosage forms comprising a swellable polymer and a high-solubility drug within the class of polymers and drugs disclosed in the '837 patent. (A1958-59 ¶¶ 127-28.) Like the '837 patent, Baveja specifically teaches using the "hydroxypropylmethylcellulose (HPMC)" polymer. (A1804-05; A1958 ¶ 127.) Baveja also identifies the precise brand of polymer as "Methocel K4M Premium (HPMC)," which has a viscosity taught by the '837 patent as useful. (A1804-05; A1817-27.) Also, like the '837 patent, Baveja teaches using high-solubility drugs with HPMC. (A1959 ¶ 128.) In particular, Baveja describes test results of oral-dosage forms made with the drugs AH and MT, both of which are within the solubility range disclosed in the '837 patent. (A1804-06.)

Both References Teach Overlapping Drug-To-Polymer Ratios: The '837 patent and Baveja both teach oral-dosage tablets having overlapping drug-to-polymer ratios. The '837 patent explains that the "weight ratio of drug to polymer in the mixture or dispersion will normally be 1:9 to 9:1." (A1822:5:3-6; A1958-59 ¶ 127.) Baveja teaches oral-dosage forms within the ratio range prescribed by the '837 patent, including AH-to-HPMC formulations with ratios of 1:2, 1:3, 1:5, and

1:6, and MT-to-HPMC formulations with ratios of 1:2, 1:2.5, 1:3, 1:4, and 1:5. (A1806.)

Both References Teach Similar Sustained-Release Profiles: The '837 patent and Baveja describe similar drug-release profiles. The '837 patent explains that "a dose of medication from the system described in the invention is specified by drug release rate, and by duration of the release. It is the continuous, controlled delivery feature of the system that allows for (a) reduced drug side effects … and (b) less frequent administration requirements." (A1822:6:53-59.) Example 26 in the '837 patent describes an oral-dosage form comprising a cellulose-based polymer and high-solubility drug "which will result in a drug delivery pattern of 8-14 hour duration." (A1825:12:21-25; A1959 ¶ 128.) Other examples in the '837 patent disclose drug release having a 4-8 hour duration. (A1824:9:50-6:13; A1826:13:40-45; A1982 ¶ 184.)

Similarly, Baveja teaches that, for oral-dosage forms comprising HPMC and a high-solubility drug, "the rate of release decreased with time and this may be due to an increase in diffusional path length for the drug which in turn may be due to slower erosion [] of the rubbery layer and faster advancement of swelling front into the glassy polymer." (A1806.) Baveja then provides graphs illustrating drug-release profiles that are within the 8-14 hour duration taught expressly by the '837 patent. Figure 1 shows the drug-release profile of a dosage form consisting of

HPMC and the highly soluble drug AH, with results provided for various drug-to-polymer ratios. (A1944 ¶¶ 85-86.)

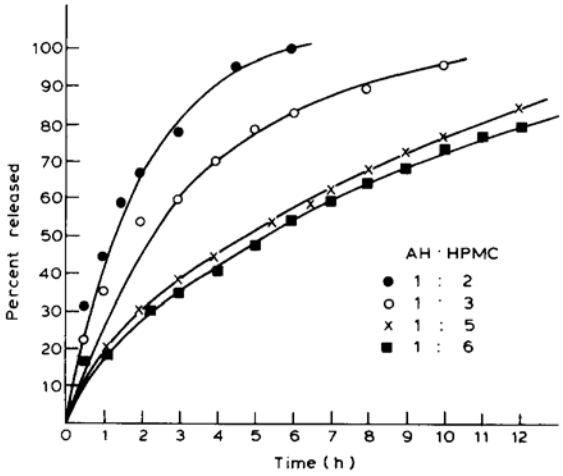

Fig. 1. Release of alprenolol hydrochloride (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

(A1806.) Figure 2 shows the drug-release profile of a dosage form consisting of HPMC and the highly soluble drug MT, with results provided for various drug-to-polymer ratios.

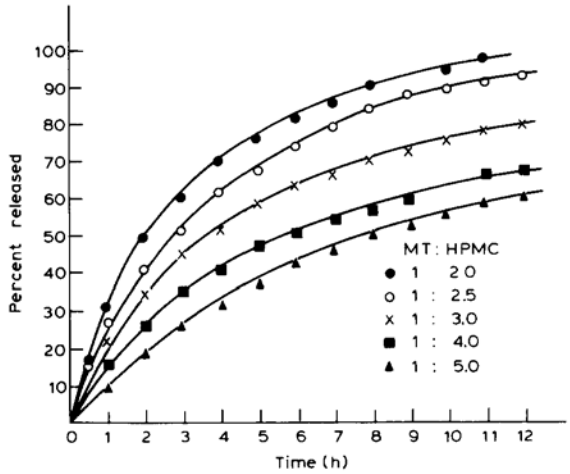

Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

(A1806.)

Moreover, the '837 patent and Baveja both teach releasing the drug by dissolution and diffusion. (A1817:Abstract ("[i]mbibed water from the gastric fluid dissolves the drug entrapped in the particles and the resulting solution diffuses from the dispersed particles"); A1804-05 (describing an "increase in diffusional path length"); A1981 ¶ 182.)

* * * *

Put simply, the '837 patent and Baveja are a classic example of "interrelated teachings of multiple [references]" providing a reason to combine them. *KSR*, 550 U.S. at 418. The complementary teachings of the two references "specifically described structures and properties that guide[]" a POSITA to dosage forms "with similar structures that would fall within the scope of the [] patent's claims." *Allergan, Inc. v. Apotex Inc*., 754 F.3d 952, 965 (Fed. Cir. 2014). The '837 patent discloses a detailed methodology for practicing the claimed inventions and expressly suggests using the types of swellable polymers, highly soluble drugs, and drug-to-polymer ratios covered by the challenged claims. For its part, Baveja describes an oral-dosage form using a specific polymer and drug from within the classes of polymers and drugs disclosed by the '837 patent. (A1958-59 ¶¶ 127-28.) Baveja also uses a drug-to-polymer ratio that is within the range disclosed by the '837 patent, and uses the same direct-compression manufacturing technique

disclosed in the ’837 patent. Baveja further describes precise drug-release profiles achieved by using the dosage forms disclosed by the ’837 patent. In such cases, a POSITA would “be able to fit the teachings of multiple patents together like pieces of a puzzle.” *KSR*, 550 U.S. at 420.

This conclusion is cemented by the high skill level of a POSITA, who would have had a Ph.D. in pharmaceutical sciences and industry experience developing oral-dosage formulations. The higher the skill level, the more likely the POSITA would find an invention obvious. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1366 (Fed. Cir. 2012).

Indeed, if there is any viability to the Supreme Court’s rule that a motivation to combine prior art may come from “look[ing] to interrelated teachings,” it compels the conclusion that a POSITA would have combined the ’837 patent and Baveja. Even when addressing prior-art references from unrelated endeavors, this Court holds that a POSITA would have a motivation to combine when a reference “‘logically would have commended itself to an inventor’s attention in considering his problem.’” *Innovention Toys, LLC v. MGA Entm’t, Inc.*, 637 F.3d 1314, 1321-22 (Fed. Cir. 2011). This reasoning applies with even greater force here given the symbiotic relationship between the ’837 patent and Baveja. *See Scientific Plastic Prods., Inc. v. Biotage AB*, 766 F.3d 1355, 1359 (Fed. Cir. 2014) (“‘If a reference disclosure has the same purpose as the claimed invention, the reference relates to

the same problem, and that fact supports the use of that reference in an obviousness rejection.'"). Given their similarities, combining the '837 patent and Baveja would require no more than "common sense" and the exercise of "ordinary creativity." *KSR*, 550 U.S. at 421.

B. The Interrelated Teachings Of The '837 Patent, Baveja, Colombo, Kim, And The '125 Patent Provide The Reason To Combine The References To Obtain The Remaining Dependent Claims

The Board correctly determined that each limitation of the challenged claims is disclosed by the '837 patent and Baveja, except for certain details recited in dependent claim 10 of the '475 and '280 patents and dependent claims 54-55, 62, and 66 of the '475 patent. The specific details recited in these dependent claims are disclosed in Colombo, Kim, and the '125 patent.

The Board found that "Kim teaches the additional limitation of claim 10" of the '475 and '280 patents, which recites that the "polymeric matrix is formed of PEO at a molecular weight of at least about 4,000,000." (A31-32; A67-68.) The Board also found that the '125 patent "teaches a drug dosage form comprising a drug and PEO having a molecular weight of 5,000,000" (A105), which satisfies the details recited in claims 54 and 55 of the '475 patent, requiring that the "solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000" (claim 54) and "a molecular weight of from about 4,500,000 to about 10,000,000" (claim 55). Claims 62 and 66 of the '475 patent recite a

viscosity range for the HPMC polymer. (A1702:27:8-11 & 27:23-26.) Colombo discloses HPMC within that viscosity range. (A15647 ¶ 110; A30147-48 ¶ 110.)

Despite the disclosure of these references, the Board erroneously concluded that claim 10 of both patents and claims 54-55, 62, and 66 of the '475 patent would not have been obvious because a POSITA would not have combined the '837 patent and Baveja with a reasonable expectation of success. (A31-32; A68-69; A104-05.) For the reasons set forth above in Part I.A, these conclusions are erroneous and should be reversed. Further, as explained below, a POSITA would have been motivated to combine the '837 patent and Baveja with Kim, Colombo, and the '125 patent, given the references' closely related teachings. These references pertain to the same field, use the same types of polymers and soluble drugs, and teach overlapping drug-to-polymer ratios and similar sustained-release profiles.

The References Pertain To The Same Field: Colombo, Kim, and the '125 patent relate to the same specialized field of endeavor as the '837 patent and Baveja. Colombo states that "swellable matrices, as drug delivery systems, exhibit anomalous release kinetics … and are suitable forms for release control in oral drug administration." (A1811.) Kim and the '125 patent teach that "[h]ydrophilic polymers … have [] been investigated for controlled drug release." (A2008; A2540:1:50-51.) Kim discloses that hydrophilic "PEO material, like HPMC, may

be a good candidate for oral drug delivery systems" that control the release of high-solubility drugs. (A2010; A15664-65 ¶ 155.) The '125 patent "provides a controlled release tablet including a pharmaceutical agent and an excipient. The excipient includes at least about 50% of a water swellable polymer." (A2540:1:61-64.)

The References Teach Using The Same Types of Polymers and Soluble Drugs: Colombo, Kim, and the '125 patent use the same types of polymers and same types of drugs as the '837 patent and Baveja. Colombo's formulations comprise HPMC to control the release of diltiazem. (A1811-16; A1947 ¶ 90.) Kim teaches that "PEO material, like HPMC, may be a good candidate for oral drug delivery systems." (A2010; A15664-65 ¶ 155.) And the '125 patent discloses that "[p]olymers of choice include uncrosslinked poly(ethylene oxide) (PEO) and hydroxypropylmethylcellulose (HPMC)." (A2541:4:18-27; A30146 ¶ 106.) Also, like Colombo, Kim and the '125 patent use diltiazem as the model drug. (A2008; A2542:6:35-36.)

The References Teach Overlapping Drug-To-Polymer Ratios: Colombo, Kim, and the '125 patent teach oral-dosage tablets having similar drug-to-polymer ratios as the '837 patent and Baveja. Colombo discloses tablets with a drug-to-polymer weight ratio of about 1:1 (A1812; A1947 ¶ 91), and Kim and the '125

patent disclose dosage forms with a drug-to-polymer weight ratio of 1:4. (A2010, Fig. 4; A2512-13, Figs. 4-5; A1971 ¶ 159.)

The References Teach The Same Sustained-Release Profiles: Colombo, Kim, and the '125 patent describe similar drug-release profiles as in the '837 patent and Baveja. All three references provide graphs illustrating drug release profiles of high-solubility drugs that are within the 8-14 hour duration disclosed by the '837 patent and Baveja. (A1814; Fig. 5; A2512-13, Figs. 4-5; A2010, Fig. 4.)

In short, as with the independent claims, combining the '837 patent and Baveja with the secondary prior-art references to achieve the challenged dependent claims would require no more than "common sense" and "ordinary creativity." *KSR*, 550 U.S. at 421. (A1972 ¶ 160.)

C. The Board Erred By Applying The Same Rigid Standard For Motivation To Combine That *KSR* And This Court Have Rejected

The combined, mutually reinforcing teachings of the complementary '837 patent and Baveja (as well as those of the secondary prior art) should have been enough for the Board to find the challenged claims obvious. Instead, however, the Board found those combinations wanting: "Although the references may have interrelated teachings, . . . Petitioner has not explained persuasively *how* or *why* a [POSITA] would have combined the 'swelling' and 'substantially intact' features of the '837 patent with the dosage formulation of Baveja." (A26; A63; A100-01.)

To the extent that the Board's "how or why" ruling reflected a finding that Purdue's evidence was conclusory, *see Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 & n.3 (Fed. Cir. 2008), such a finding would be unsupported by substantial evidence. Purdue's evidence was complete and extensive: Dr. Bodmeier testified that the '837 patent discloses administering, during the fed mode, a dosage form containing an alkyl-substituted cellulose (which includes HPMC), that swells, is retained in the stomach, and maintains its physical integrity over at least a substantial portion of the time period during which the active ingredient (which includes freely soluble drugs) is released into the stomach. (A1929 ¶ 48.) Dr. Bodmeier also testified as to "why" a POSITA would combine the teaching of the '837 patent and Baveja to obtain the "swellable" and "substantially intact" limitations: "to formulate a swellable, controlled release oral-dosage form for releasing a high-solubility drug with particular release kinetics that will remain substantially intact and be retained in the stomach during the fed mode." (A1961 ¶ 131.) Finally, Dr. Bodmeier testified that Baveja teaches "how" to achieve the "particular release kinetics" of HPMC formulations containing high-solubility drugs to obtain the same two limitations. (A1927-28 ¶ 44.) In particular, Dr. Bodmeier testified that the test results set forth in Baveja demonstrate the well-known formulation principle that increasing the concentration or molecular weight of HPMC (the rate-controlling polymer) will

slow down the rate of drug release. (A1976 ¶ 169.) Accordingly, to the extent that the Board considered Purdue's evidentiary submission inadequate, such a holding is unsustainable: Purdue's evidence clearly established "how and why" a POSITA would combine the teachings of Baveja and the '837 patent.

More glaringly, however, the Board's "how or why" ruling reflected an unduly rigid view of where the motivation to combine references may be found. In holding Purdue's case of obviousness deficient, the Board dismissed all of the indicators of a motivation to combine that are contained in the prior art itself, *see Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013), not to mention "the very nature of the subject matter involved," *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). Instead, the Board demanded that Purdue's proof satisfy an overly exacting standard, failing to appreciate the obvious overlap between the '837 patent and Baveja. This was legal error. Although the Board cited *KSR*, its analysis failed to adhere to the flexible legal principles set forth by the Supreme Court and this Court's precedent. *See Ball Aerosol & Specialty Container, Inc. v. Limited Brands, Inc.*, 555 F.3d 984, 993 (Fed. Cir. 2009) (reversing holding of non-obviousness because "[a]lthough the court quoted *KSR* at length, it misconstrued the language").

In *KSR*, the Supreme Court repudiated the formalistic standard that the Board applied here, directing courts to avoid "overemphasis on the importance

of … the explicit content" of prior-art references. 550 U.S. at 419. The obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. Here, the references themselves—indeed, their very subject matter—demonstrate on their faces that a POSITA would have "combined the 'swelling' and 'substantially intact' features of the '837 patent with the dosage formulation of Baveja." (A26; A63; A100-01.)

The '837 patent teaches that an oral-dosage form will "*swell to a size which promotes retention*" (A1820:1:45-47; A1979 ¶ 178) and will "*maintain[] its physical integrity* over at least a substantial portion of the time period during which the drug is released into the stomach" (A1820:2:7-9; A1958 ¶ 126), when the oral-dosage form comprises: (1) cellulose-based polymers, such as HPMC (A1820:1:58-64; A1825:11:24-25; A1827:16:25-26); (2) a drug having a solubility "range of 0.01% to about 35%" (A1820:2:35-38); and (3) a drug-to-polymer ratio of 1:9 to 9:1 (A1822:5:3-6).

Baveja fits into the '837 patent's teachings hand-in-glove. It uses oral-dosage forms comprising HPMC, drugs within the 0.01% to 35% solubility range, and drug-to-polymer ratios within the 1:9 to 9:1 range. The '837 patent therefore confirms that the oral-dosage forms used in Baveja will "swell[]" and remain

"substantially intact." (A1961-62 ¶¶ 132-33.) In fact, the first page of Baveja identifies a list of "key words" in the article that include "HPMC" and "swellable matrix tablet" (A1804), demonstrating that a POSITA would not have needed to read past the first page of Baveja to ascertain its combinability with the '837 patent. The Board's error thus was "the result of not reading the prior art for all that it teaches." *Smith & Nephew*, 721 F.3d at 1378.

The Board's improper formalism also ignores the basic, common-sense rule that when, as here, "a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. "[T]he presumption [] that similar compositions have similar properties" is "well settled" law. *See, e.g.*, *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 976 (Fed. Cir. 2014); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Here, given that oral-dosage forms in the '837 patent comprising HPMC, a drug with solubility "in the range of 0.01% to about 35%," and a drug-to-polymer ratio of 1:9 to 9:1 achieve performance characteristics of swelling to promote gastric retention and remaining substantially intact, a POSITA would have known both "how" and "why" to combine Baveja with the '837 patent to achieve the same performance characteristics in a dosage form having the kinetic properties set forth in Figures 1 and 2 of Baveja. (A1961-

62 ¶¶ 132-33.) Indeed, such performance characteristics would be the natural result of Baveja's dosage form, since it shared the same or similar parameters (polymer, drug solubility, and drug-to-polymer ratio) disclosed in the '837 patent. *See Amgen Inc. v. Hoechst Marion Roussel, Inc*., 314 F.3d 1313, 1355 (Fed. Cir. 2003) (noting presumption "that both the claimed and unclaimed disclosures in a prior art patent are enabled"). The same holds true for Colombo, Kim, and the '125 patent, which teach using the same polymers and identify the specific molecular weight and viscosity properties of the polymer.

In short, the record is replete with evidence that, under the correct "common-sense" standard set by *KSR* and its progeny from this Court, demonstrates that a POSITA would have successfully combined the '837 patent, Baveja, and the secondary prior art to yield the invention claimed in the Depomed patents.

D. The Problem To Be Solved Provides A Further Reason To Combine The '837 Patent And Baveja

"One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 419-20. "Under the correct analysis, *any need or problem known in the field* of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id*. at 420. This Court "ha[s]

consistently stated that courts 'may find a motivation to combine prior art references in the nature of the problem to be solved.'" *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011). Here, although the Board acknowledged that the "nature of the problem to be solved" can provide a reason to combine the prior art, it ultimately misapplied this rule. (A23-24; A60-61; A98-99.)

Before the Board, Purdue identified the problem to be solved as "formulat[ing] a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." (A25; A62; A99; A1961¶ 131.) Without providing any analysis of the basis for Purdue's definition, and reversing course from its institution decisions, the Board concluded that "Petitioner's recitation of the nature of the problem to be solved is essentially a recitation of [the challenged] claim[s]." (A27; A64; A101-02.) However, the four corners of the prior-art '837 patent demonstrate the Board's error. *See Smith & Nephew*, 721 F.3d at 1377-78 (reversing Board's decision for "overlook[ing]" and "ignor[ing]" a reference's substantive teaching). The table on the following page demonstrates that Purdue's definition of the problem to be solved comes directly from the problem addressed by the prior-art '837 patent.

Purdue's Definition of the Nature of the Problem	**The '837 Patent**
Formulating [1] a swellable, controlled release oral dosage form for releasing a drug	[1] "A **sustained release oral drug dosage form for releasing** a solution of a drug into the stomach" that will "**swell**[] unrestrained dimensionally" (A1826:13:65-66; A1820:1:58-63 (the sustained-release oral dosage form "swells unrestricted dimensionally").)
[2] with particular release kinetics and	[2] "[A] dose of medication from the system described in the invention is specified by **drug release rate, and by duration of the release**. It is the continuous, controlled delivery feature of the system that allows for (a) reduced drug side effects … and (b) less frequent administration requirements." (A1822:6:52-59; A1825:12:21-25.)
[3] that will remain substantially intact and	[3] "The invention is a sustained-release oral drug dosage form … [that] **maintains its physical integrity** over at least a substantial portion of the time period during which the drug is released into the stomach and then dissolves." (A1820:1:58-2:9; A1821:4:42-46.)
[4] be retained in the stomach during the fed mode.	[4] "The invention is a sustained-release oral drug dosage form for releasing a solution of a **drug into the stomach** … that (i) swells unrestricted dimensionally via imbibition of water from gastric fluid to increase the size of the of particles to promote gastric retention of the pellets **in fed mode** induced patients." (A1820:1:58-65.) "The swollen particles will be of a size that promotes their **retention in the stomach** when the patient is not in the fed mode (i.e., presence of food) and particularly **when the patient is in the fed mode**." (A1822:5:9-12.)

The fact that the '837 patent addresses the same problem as the challenged claims of the '475 and '280 patents is not surprising, given that all three patents have the same lead inventor (John Shell) and the same assignee (Depomed). All three patents also relate to the same specific field of pharmacology—formulating sustained-release drug dosage forms. The '837 patent states that "[t]he invention is in the general field of pharmacology and relates specifically to alkyl-substituted cellulose-based *sustained-release drug dosage forms*…." (A1820:1:17-22.) The '475 and '280 patents state that their "invention is in the general field of pharmacology, and relates in particular to *formulations for drugs that benefit from a prolonged time of controlled release* in the stomach and upper gastrointestinal (GI) tract…."). (A144:1:11-14; A119:1:12-15.)

Rather than focusing on the content of the '837 patent as the basis for Purdue's definition of the problem to be solved, the Board attributed the similarity between Purdue's definition and the claims of the '475 and '280 patents to "a hindsight bias." (A34; A70; A102.) The Board's cursory conclusion rests on the same error corrected by *KSR*. "Rigid preventative rules … are neither necessary under our case law nor consistent with it." *KSR*, 550 U.S. at 421. As this Court has explained, the "warning" against hindsight "*does not provide a rule of law* that an express, written motivation to combine must appear in prior art references before a finding of obviousness…. [T]his court has consistently stated that a

court … may find a motivation to combine prior art references in the nature of the problem to be solved." *Ruiz v. A.B. Chance Co*., 357 F.3d 1270, 1276 (Fed. Cir. 2004). To that end, the "anti-hindsight jurisprudence is a test that rests on the unremarkable premise that legal determinations of obviousness … *should be based on evidence* rather than on mere speculation of conjecture." *Alza*, 464 F.3d at 1290. As shown in the table above, the record evidence unmistakably establishes that Purdue's definition of the problem to be solved is based entirely on the prior-art '837 patent, and not a hindsight review of the challenged claims. Indeed, "the references in the case go *beyond* just illuminating a known problem; *they also expressly propose the claimed solution*." *Bayer*, 713 F.3d at 1375-76.

The Board's error in analyzing the "nature of the problem to be solved" is underscored by the disconnect between its institution decisions and its Final Written Decisions. When instituting the IPR proceedings, the Board determined that:

> A [POSITA] would have a reason to combine Baveja, the '837 patent, and the '548 patent given the nature of the problem to be solved: "to formulate a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode."

(A340; A14700; A28809.) Nothing about the content and teachings of the prior art changed between the Board's institution decisions and its Final Written Decisions. Accordingly, the Board's reliance on this Court's "recen[t] remind[er]"

in *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853 (Fed. Cir. 2015) ("defining the problem in terms of its solution reveals improper hindsight in the selection of prior art relevant to obviousness") (A27; A64; A102) had no relevance to this case—as the Board's own institution decisions revealed, the "problem to be solved" came from the prior art, not from the Depomed patents.

The Board's confusion is perhaps understandable in view of the virtual identity of the claimed Depomed invention to the teachings of the prior art, but that is exactly the reason that the Board should have found—and why this Court should hold—that the Depomed patents are obvious.

II. UNDER THE PROPER LEGAL STANDARD, THE RECORD ESTABLISHES THAT A POSITA WOULD HAVE HAD A REASONABLE LIKELIHOOD OF SUCCESS

The Board concluded that even if Purdue had shown a motivation to combine, it had not "established that a [POSITA] would have had a reasonable expectation of success in doing so." (A28; A65; A102-03.) Similar to its flawed analysis of the reasons to combine, the Board's erroneous conclusion regarding reasonable expectation of success stems from applying the wrong legal standard.

Obviousness does not demand "a guarantee" or "absolute certainty for success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *Par Pharm.*, 773 F.3d at 1198. Rather, the inquiry is whether a POSITA "would have perceived a *reasonable* expectation of success in making the invention in light of

the prior art." *Amgen Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). Here, Baveja's identification of specific parameters for making dosage forms and its test results based on those dosage forms confirms that a POSITA would have had a reasonable expectation of success in combining the '837 patent and Baveja.

A. Baveja And The '837 Patent Establish A Reasonable Expectation Of Success

For purposes of "reasonable expectation of success," what "matter[s] is whether the prior art gives direction as to *what parameters are critical and which of the many possible choices may be successful*." *Allergan*, 754 F.3d at 965. The '837 patent and Baveja do precisely that.

The critical parameters to consider when formulating a dosage form that will swell, remain intact, and control the release of drug, as taught by the '837 patent, are (1) the type of polymer; (2) the type of dosage form; (3) the solubility of the drug; and (4) the drug-to-polymer ratio. The '837 patent teaches oral-dosage forms that will "swell[] unrestricted dimensionally" and "maintain[] [ ] physical integrity over at least a substantial portion of the time period during which the drug is released" (A1820:1:58-2:10) when they comprise: (1) a cellulose-based polymer such as HPMC (A1825:11:24-25; A1825:11:39-43); (2) a drug having a solubility "in the range of 0.01% to about 35% by weight" (A1820:2:35-38); and (3) a drug-to-polymer ratio ranging from "1:9 to 9:1" (A1822:5:3-5). As explained, the '837

patent teaches this combination, reciting broad classes of polymers and drugs. (A1820:1:39-41.) The '837 patent also teaches specific formulations, including dosage forms that control the release of high-solubility drugs. (A1825:12:19-34; A1959 ¶ 128.) Thus, the '837 patent provides clear direction as to *what parameters are critical and which of the many possible choices may be successful*.

Further, Baveja describes dosage forms that fall within the parameters suggested by the '837 patent, including HPMC in particular, which is one of the "preferred alkyl-substituted celluloses" in the '475 and '280 patents. (A122:8:17-20.) Moreover, the HPMC in Baveja has a viscosity of 4,000 centipoise, which is another "prefer[ence]" in the '475 and '280 patents (A122:8:17-20; A1940 ¶ 75), and as taught by the '837 patent, is suitable for use in the dosage forms described in that patent that swell to promote retention and remain intact. (A1821:4:61-63.) Baveja's dosage forms also include specific drugs (AH and MT) having solubilities within the range suggested by the '837 patent. (A1804-06; A1959 ¶ 128.) Baveja's dosage forms also have specific drug-to-polymer ratios within the range suggested by the '837 patent. (A1806; A1958 ¶ 127.) Further, Baveja explains that the tested dosage forms were made the same way as in the '837 patent—direct compression into tablets. (A1805; A1820:1:38-41.)

Consistent with the teachings of the '837 patent, Baveja reports test results showing dosage forms that swell and provide sustained drug release. (A1806.)

Figures 1-2 show drug-release profiles within the range described by the '837 patent. (*Compare* A1806 *with* A1825:12:21-25.) Thus, while "[c]onclusive proof" of success "is not necessary," *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014), Baveja goes even further by demonstrating *actual success* of dosage forms made in the same way and formulated according to the same parameters disclosed by the '837 patent. (A1805-06.)

Moreover, Purdue's expert Dr. Kinam Park manufactured dosage forms according to Baveja's disclosure, and conducted swelling and dissolution tests as described in the patents-at-issue. (A2012-45.) The results confirmed that the dosage forms swelled to a size that would promote retention during the fed mode and remained substantially intact until all of the drug was released, while satisfying the release-kinetic limitations set forth in the patents-at-issue. (A1942-43 ¶ 82; A1945 ¶ 87; A1946 ¶ 89.)

Given the specific teachings and reported results in Baveja and the '837 patent, this case stands in stark contrast to circumstances where there was no reasonable expectation of success because the prior art "'gave [] no indication of which parameters were critical'" or "'gave only general guidance as to the particular form of the invention or how to achieve it.'" *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007). The '837 patent and Baveja identify the specific manner for making dosage forms, the specific

parameters for formulating those dosage forms (including the specific polymer, specific drugs, and specific drug-to-polymer ratios), the specific drug-release profiles, and the specific properties covered by the challenged claims. These disclosures provide far more than "sufficient guidance as to what parameters would lead to a reasonable expectation of success." *Allergan*, 754 F.3d at 965.

B. By Applying The Wrong Standard, The Board Reached The Wrong Conclusion Regarding Reasonable Expectation Of Success

The Board concluded that there was no reasonable expectation of success because there was some level of unpredictability due to "the number of formulation considerations at play when preparing a drug formulation." (A29; A65; A103.) That is the wrong standard. This Court has rejected the "rule of law equating unpredictability to patentability," explaining that "[t]his cannot be the proper standard since the expectation of success need only be reasonable, not absolute." *Pfizer*, 480 F.3d at 1364. Accordingly, even if there were "some degree of unpredictability" in combining the '837 patent and Baveja, that cannot defeat obviousness because "the mere possibility that some [dosage forms] may not [work as claimed] does not demand a conclusion that those that do are necessarily non-obvious." *Id.* at 1366.

Contrary to the Board's conclusion, the possibility that some testing may have been necessary to achieve the claimed invention does not show an absence of a reasonable expectation of success. (A29; A65; A103.) Dr. Bodmeier established

that modifying the release rates, swelling, and gastric-retentive properties of the formulations disclosed in Baveja and the '837 patent would have been a matter of routine experimentation. (A1925-29 ¶¶ 41-49; A1935-37 ¶¶ 61-66; A1957 ¶ 125.) This is confirmed by the fact that the level of detail and guidance in the '837 patent is the same as in the '475 and '280 patents. Thus, the '837 patent would have enabled a POSITA to practice the challenged claims. *Amgen*, 314 F.3d at 1355. This Court's precedent establishes that routine experimentation based on prior-art disclosures cannot save claims from obviousness. *See Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1349 n.2 (Fed. Cir. 2009) ("Such experimentation is routine and cannot render an otherwise obvious claim valid."); *Pfizer*, 480 F.3d at 1368 ("The experimentation needed, then, to arrive at the subject matter claimed … was 'nothing more than routine' application of a well-known problem-solving strategy, and we conclude, 'the work of a skilled artisan, not of an inventor.'").

The Board's conclusion also suffers from the same defect that the Supreme Court addressed in *KSR*: "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'…. [T]he fact that a combination was obvious to try might show that it was obvious under § 103." 550 U.S. at 421. Here, a highly skilled POSITA armed with the '837 patent and Baveja would have "had every motivation to seek and every reasonable

expectation of success in achieving the … the claimed invention." *Kubin*, 561 F.3d at 1361. Indeed, the '837 patent established that its disclosed dosage form would "swell" and "maintain[] its physical integrity." (A1820:1:58-2:10.) And Baveja confirmed that such dosage forms swell and attain the desired drug-release profiles. (A1804-06.)

The Board also erred in concluding that Purdue did not identify "any combinations of Baveja and the '837 patent that would be most promising to try." (A29; A66; A104.) Baveja describes a dosage form formulated using a specific type of HPMC, specific high-solubility drugs, and specific drug-to-polymer ratios. Baveja also reports that the specific dosage forms "swelled," and Figures 1-2 depict drug-release profiles suggested by the '837 patent and that fall within the claims of the '475 and '280 patents. (A1805-06.) Therefore, *Baveja itself* describes those "promising" formulations and reports successful test results based on such formulations.

Moreover, a reasonable expectation of success does not require identifying the best or "most promising" options to try. A POSITA need only have a reasonable expectation of success of formulating any dosage form that is within the scope of thousands of dosage forms covered by the challenged claims. "Given the breadth of the [challenged] patent's claimed invention, appellants did not have the exacting burden of showing a reasonable expectation of success" for all dosage

forms within the scope of the claims nor any preferred dosage forms. *Allergan*, 754 F.3d at 963. Purdue "instead had the burden of showing *that any* compounds within the broad genus claimed by the [challenged] patent[s], including those [disclosed by Baveja] … were obvious at the time of the invention." *Id*. The same reasoning and result apply to Colombo, Kim, and the '125 patent that teach dosage forms comprising the same types of polymers and highly soluble drugs as the '837 patent and Baveja.

C. The Board Erred As A Matter Of Law By Relying On Inventor Helm's And Dr. Hopfenberg's Testimony To Conclude That There Was No Reasonable Expectation of Success

The Board erred by relying on the testimony of inventor Helm and Dr. Hopfenberg to conclude there was no reasonable expectation of success. As explained below, both witnesses' testimony was legally irrelevant.

1. Inventor Helm's Testimony Is Legally Irrelevant Because She Was Not Aware Of The Prior Art

The obviousness "analysis is objective." *KSR*, 550 U.S. at 406. "Whatever [an actual person] did or did not *personally* realize at the time [of invention] based on actual knowledge is irrelevant. The relevant inquiry is what a [POSITA] would have gleaned from the cited references at the time." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1364 (Fed. Cir. 2001). Contrary to these principles, the Board concluded that a POSITA would not have had a reasonable expectation of success by relying on inventor Helm's testimony that it

"took [her] years of research and testing in the laboratory to manipulate different variables … to come up with the claimed invention." (A25-26; A62; A100.) This was legal error. The "question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." *KSR*, 550 U.S. at 420; *see Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]bviousness is determined *entirely* with reference to a *hypothetical* [POSITA].").

Moreover, inventor Helm does not qualify as a POSITA (A9647-48 ¶ 3), and her testimony was not probative of a POSITA's knowledge. The "legal construct" of a POSITA "*presumes that all prior art references* in the field of the invention *are available* to this hypothetical skilled artisan." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). A POSITA therefore has "knowledge" of all the prior art. *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991). But Ms. Helm testified that when she worked on developing the claimed subject matter, she was wholly unaware of the prior-art references—she admitted that she did not use the prior art during her research (A3569:17:12-17), "did not do literature searches" (A3571:22:23-23:2), "didn't actually look at the literature" (A3573:33:22-34:2), and had no recollection of ever seeing the Baveja reference. (A3580:61:19-62:19.) Rather, "the only thing [Ms. Helm] did was to talk to the manufacturers of the polymers." (A3569:17:12-17.)

Ms. Helm's testimony has no bearing on the obviousness analysis: while a POSITA is presumed to know all the pertinent prior art, Ms. Helm was actually ignorant of it. The Board thus legally erred by using Ms. Helm as a proxy for a POSITA. "That presumed knowledge was, of course, available to all. *It is irrelevant whether or not [the inventor] was aware of it*." *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985).

2. Dr. Hopfenberg's Testimony Is Legally Irrelevant Because It Fails To Take Into Account The Teachings Of The '837 Patent And Baveja

In concluding that there was no reasonable expectation of success, the Board also relied on its view that "both parties' declarants testified about the number of formulation considerations at play when preparing a drug formulation." (A29; A65-66; A103.) However, Depomed's expert Dr. Hopfenberg's testimony that "a vast array of structural limitations affect polymer and matrix properties" fails for the same reason as inventor Helm's testimony. Dr. Hopfenberg's testimony was not related to, or concerned with, the particular teachings of the '837 patent and Baveja. (A:29; A9340-41 ¶ 59; A9390-91 ¶ 161.) He failed to take into account Baveja's identification of a specific brand of HPMC polymer, specific types of high-solubility drugs, specific drug-to-polymer ratios, and the specific manufacturing process. Instead, Dr. Hopfenberg mused on how a POSITA would go about creating an oral-dosage form from scratch. His testimony ignored that a

POSITA would have had knowledge of the detailed teachings of the '837 patent and Baveja, which would have narrowed the possible combinations substantially just as a matter of sheer mathematics.

The obviousness analysis, however, does not start from "a blank slate." *KSR*, 550 U.S. at 424. As this Court explained when reversing a holding of non-obviousness, "it does not matter whether hair growth is *generally* an unpredictable endeavor—the question is more narrowly whether the success of using selective PGF analogs to treat hair loss would be reasonably unpredictable.... Once [the prior-art reference] was published, the general characteristics of the hair growth art ceased to be relevant [because the prior-art reference] taught that PGF analogs could be used to grow hair." *Allergan*, 754 F.3d at 965 (emphasis in original).

As for the testimony of Purdue's expert Dr. Bodmeier invoked by the Board (A29; A65-66; A103), when read in context, his reference to various considerations for oral-dosage formulations addresses a circumstance where the dosage form has not been disclosed. "Th[is] Court has emphasized that 'substantial evidence' review involves examination of the *record as a whole*, taking into account evidence that both justifies and detracts from an agency's decision." *Gartside*, 203 F.3d at 1312. Here, Dr. Bodmeier explained that the different considerations identified in his declaration do not apply when, as with Baveja, specific polymers and drugs have been selected:

> Q: So given that you listed nine different parameters in paragraph 41 of your declaration, are there additional parameters that you would consider in coming up with a polymer formulation that are not listed here?
>
> A: Well, maybe I need to clarify myself. There are nine parameters listed there, but the excipient suppliers, they don't give you that much flexibility. So if you do a controlled release dosage form, *you usually have a high molecular* [*weight*] *HPMC* [*grade*] *in it*. You may mix it. These are the major effect, *particle size is fixed*. You can only buy the grade in a certain particle size. *Chemical substitution is fixed*. There's also no choice you have. So a formulator can play with some molecular weight and the polymer content. And these are the parameters which one changes. So others really have minor effect. A lot easier to handle.
>
> Q: So the recipient manufacturers set certain of these parameters, and you as a formulator would not have the flexibility to change that; is that correct?
>
> A: That is correct. So, if you're saying okay, I want HPMC with a certain chemical substitution, you don't have that choice, because you have to buy what is provided by the supplier.

(A2818-19:65:7-66:14; A2883.)

Indeed, the considerations identified in Dr. Bodmeier's declaration and cited by the Board—"molecular weight, chemical substitution, particle size, hydration rate effect, polymer content, dosage form, dosage size and manufacturing processes" (A29; A65-66; A103)—were already taught and specified by Baveja. Baveja identifies the specific brand of HPMC—Methocel K4M Premium—and its supplier—Colorcon Ltd. (A1805.) This fact addresses considerations concerning molecular weight, chemical substitution, and hydration-rate effect. Baveja also

identifies specific highly soluble drugs and their suppliers, which addresses the consideration regarding particle size. (A1805.) Additionally, as shown in Figures 1 and 2, Baveja teaches that an increase in polymer concentration results in a slower drug release, thus addressing the consideration of polymer content. (A1806.) Further, Baveja specifically teaches a tablet consisting of Methocel K4M Premium HPMC and either MT or AH as the high-solubility drug, thereby addressing the dosage form consideration. Baveja also identifies two dosage sizes used in the dosage form, thus addressing the dosage size consideration. (A1805.) And Baveja teaches that the dosage forms were compressed into tablets, thus addressing the manufacturing process consideration. (A1805.) Baveja therefore specifically accounts for the considerations identified in Dr. Bodmeier's declaration.

Finally, the Board failed to account for the background knowledge of a POSITA, discussed in Dr. Bodemeier's declaration, in concluding that Purdue did not "address sufficiently why a person of ordinary skill in the art would believe it could modify the formulation of Baveja to incorporate the 'swelling' and 'substantially intact' features of the '837 patent without, for example, affecting the other desired properties of the original Baveja formulation (e.g., the drug release profile)." (A29.) At the time of the alleged invention, the swelling properties of HPMC polymers were well known. It was also well known that increasing the

viscosity or concentration of the polymer in a formulation strengthens the matrix so that it would remain intact. (A1927; A2209.) Countless references taught that the greater the polymer's viscosity, the more resistant the dosage form was to erosion. (A1952; A2148; A2140; A2231-32; A2194-2228.) It was also common knowledge to a POSITA that "the effects of polymer concentration and viscosity on drug release rates are interrelated and can be predicted." (A1952; A2209; A1806, Figs. 1-3.) Accordingly, a POSITA would have had a reasonable expectation of success of adjusting the viscosity and concentration of a polymer such that the dosage form will remain substantially intact while maintaining the desired release rate.

* * * *

It bears repeating that, in this case, a POSITA would not be working from "a blank slate." *KSR*, 550 U.S. at 424. Rather, Baveja describes a specific manufacturing process and provides detailed parameters for formulating the dosage forms recited in the challenged claims. Baveja also reports test results showing that the dosage forms swelled and achieved drug-release profiles within the time durations suggested by the '837 patent. Moreover, Baveja uses the specific polymer (HPMC) and the same parameters that the '837 patent teaches will result in an oral-dosage form that "swells unrestricted dimensionally" and "maintains its physical integrity over at least a substantial portion of the time period during which

the drug is released into the stomach." (A1820:1:58-2:9.) Accordingly, a POSITA who read the interrelated teachings of the '837 patent and Baveja would have had every reason to combine the teachings and expect the combination to be a successful, swellable, controlled-release dosage form with all of the characteristics of the challenged claims.

CONCLUSION

The Board's holdings should be reversed and the challenged claims held to be unpatentable.

Dated: October 5, 2015

Respectfully submitted,

/s/ Gregory A. Castanias

GREGORY A. CASTANIAS
JENNIFER L. SWIZE
JONES DAY
51 Louisiana Avenue NW
Washington, D.C. 20001
(202) 879-3939
gcastanias@jonesday.com
jswize@jonesday.com

JOHN J. NORMILE
GASPER J. LARosa
LISAMARIE LOGIUDICE
JONES DAY
222 East 41st Street
New York, NY 10017
(212) 326-3939
jjnormile@jonesday.com
gjlarosa@jonesday.com
llogiudice@jonesday.com

SASHA MAYERGOYZ
JONES DAY
77 West Wacker
Chicago, IL 60601
(312) 269-1572
smayergoyz@jonesday.com

Counsel for Appellant Purdue Pharma L.P.

ADDENDUM

Trials@uspto.gov
571-272-7822

Paper 72
Entered: July 8, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PURDUE PHARMA L.P.,
Petitioner,

v.

DEPOMED, INC.,
Patent Owner.

Case IPR2014-00377
Patent 6,635,280 B2

Before ERICA A. FRANKLIN, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Purdue Pharma L.P. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 8–15, 43, 45, and 46 of U.S. Patent No. 6,635,280 B2 (Ex. 1001, "the '280 patent"). Paper 1 ("Pet."). Depomed, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). On July 10, 2014, we instituted an *inter partes* review of claims 1, 8–10, 13–15, 43, 45, and 46 on certain grounds of unpatentability alleged in the Petition. Paper 9 ("Dec. Inst."), 25. Patent Owner timely filed a Response (Paper 24, "PO Resp."), to which Petitioner timely filed a Reply (Paper 35, "Pet. Reply").

Both parties filed motions to exclude certain exhibits and testimony. Paper 41 (Petitioner); Paper 48 (Patent Owner). Both parties opposed the other's motion to exclude. Paper 56 (Patent Owner Opposition); Paper 51 (Petitioner Opposition). And both parties filed reply briefs in support of their motions to exclude. Paper 58 (Petitioner Reply); Paper 59 (Patent Owner Reply).

Patent Owner also filed a Motion for Observation (Paper 46) on certain cross-examination testimony of Petitioner's declarant Dr. Eric M. Gaier, and Petitioner filed a Response (Paper 52).

A consolidated oral hearing for this proceeding and Cases IPR2014-00378 and IPR2014-00379 was held on March 19, 2015, a transcript of which has been entered in the record.[1] Paper 71 ("Tr.")

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[1] Petitioner and Patent Owner filed Objections to Demonstrative Exhibits. Paper 66 (Patent Owner); Paper 67 (Petitioner). In this Final Written Decision, we rely directly on the arguments presented properly in the

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 8–10, 13–15, 43, 45, and 46 of the '280 patent are unpatentable.[2]

A. Related Proceedings

Petitioner and Patent Owner identify various district court actions involving the '280 patent, including an action involving the parties titled *Depomed, Inc. v. Purdue Pharma L.P.*, No. 3:13-00571 (D.N.J.). Pet. ix; Paper 5 at 2–3.

Petitioner has also filed two related petitions for *inter partes* review of U.S. Patent No. 6,340,475 B2, which is the parent of the '280 patent. *See* IPR2014-00378, IPR2014-00379. We issue Final Written Decisions in those two related proceedings concurrently herewith.

B. The '280 Patent (Ex. 1001)

The '280 patent relates to drugs formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic polymers that swell upon imbibition of water to a size large enough to promote gastric retention of the drug during the fed mode. Ex. 1001,

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parties' briefs and the evidence of record. The demonstrative exhibits were only considered to the extent they are consistent with those arguments and evidence.

[2] On February 20, 2015, Patent Owner objected to Petitioner's use of a condensed font in Petitioner's Reply paper. Petitioner, however, appears to have used the same condensed font throughout this proceeding. *Compare* Pet. *with* Pet. Reply (using same font). In light of Patent Owner's late objection, we deem the objection to be waived.

Abstract. Drugs administered by conventional tablets generally become available to body fluids at a high rate initially, followed by a rapid decline. *Id.* at 1:31–33. To address that issue, controlled drug delivery systems were introduced in the 1970's. *Id.* at 1:35–37. Many of the controlled delivery systems utilize hydrophilic, polymeric matrices that provide controlled release of sparingly soluble drugs. According to Specification, however, such matrices do not provide adequate control of drug release for highly soluble drugs. *Id.* at 1:45–50.

The claimed invention allows drugs that are highly soluble in water to be administered orally in a way that will prolong their release rate throughout the duration of the fed mode. *Id.* at 5:32–36. This prolonged release rate reduces the problem of transient overdosing, and controls the dosage to safer and more effective levels over an extended period of time. *Id.* at 5:36–41. Moreover, the Specification states that particles exceeding about 1 cm in size are larger than the pylorus and are retained in the stomach for approximately 4 to 6 hours. *Id.* at 11:66–12:2. The Specification states that these benefits are due, in part, to using a polymeric matrix that is water-swellable rather than just hydrophilic, that has an erosion rate substantially slower than its swelling rate, and that releases the drug primarily by diffusion rather than erosion. *Id.* at 5:57–62. Preferred polymeric matrices include water-swellable polymers such as hydroxypropylmethylcellulose ("HPMC") and poly(ethylene) oxide ("PEO"). *Id.* at 7:54–8:51.

C. Illustrative Claims

Independent claims 1 and 43 are illustrative and are reproduced below:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20, said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug after such immersion, and that remains substantially intact until substantially all of said drug is released.

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

Claims	**Basis**	**References**
1, 8, 9, 13–15, 45, and 46	§ 103	Baveja,[3] the '837 patent,[4] and the '548 patent[5]
10	§ 103	Baveja, Kim,[6] the '837 patent, and the '548 patent
43	§ 103	Baveja, the '837 patent, and Colombo[7]

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279–81 (Fed. Cir. 2015). Under that standard, and absent any special definitions, we give

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[3] Baveja et al., *Zero-Order Release Hydrophilic Matrix Tablets of β-adrenergic Blockers*, 39 INT'L J. OF PHARM. 39–45 (1987) (Ex. 1008).
[4] John W. Shell, US 5,582,837, issued Dec. 10, 1996 (Ex. 1010).
[5] Edgren et al., US 4,871,548, issued Oct. 3, 1989 (Ex. 1017).
[6] Cherng-ju Kim, *Drug Release from Compressed Hydrophilic POLYOX-WSR Tablets*, 84 J. PHARM. SCIENCES 303-306 (1995) (Ex. 1019).
[7] Colombo et al., *Drug Release Modulation by Physical Restrictions of Matrix Swelling*, 63 INT'L J. OF PHARM. 43-48 (1990) (Ex. 1009).

claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. Prior Construed Claim Terms

We construed the following claim terms in the Decision to Institute.

Claim Term	**Claim(s)**	**Construction**
"gastric fluid"	1, 43	"[b]oth the fluid in the stomach and simulated or artificial fluids recognized by those skilled in the art as a suitable model for the fluid of the human stomach" (Dec. Inst. 6–7)
"releases substantially all of said drug after such immersion"	1	"[a]t least 80% of the drug has been released" (Dec. Inst. 7)
"releases substantially all of said drug within about ten hours after such immersion"	43	"at least 80% of the drug has been released after ten hours of immersion in gastric fluid" (Dec. Inst. 7)
"substantially intact"	1	"a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles" (Dec. Inst. 7–8)

Dec. Inst. 6–8.

Because nothing in the full record developed during trial persuades us to deviate from our prior constructions, we adopt those constructions for purposes of this Decision.

Two of the claim terms, however, require additional discussion at this stage of the proceeding:

2. "substantially all"

Patent Owner asserts that the term "substantially all," as it appears in various claim phrases in claims 1, 43, and 46, should be construed as "at least 80%." PO Resp. 15–16. Patent Owner notes that this construction would be consistent with our prior constructions of "releases substantially all of said drug after such immersion" and "releases substantially all of said drug within about ten hours after such immersion." Dec. Inst. 7. Petitioner does not object to Patent Owner's proposed construction in its Reply.

Based on the information presented and for the same reasons stated in our Decision to Institute (*id.*), we determine that the broadest reasonable interpretation of "substantially all" as used in the claims is "at least 80%."

3. "releases said drug . . . by the dissolution and diffusion of said drug out of said matrix"

The parties dispute the construction of the term "releases said drug . . . by the dissolution and diffusion of said drug out of said matrix" (i.e., the "dissolution and diffusion" limitation) in claim 1. We did not construe this term in the Decision to Institute for this proceeding. As Petitioner notes, however, we construed this term in related case IPR2014-00656, which also involves the '280 patent. Pet. Reply 1. In the Decision to Institute in that case, we preliminarily construed the term according to its plain and ordinary meaning and declined to limit claim 1 to require that drug release occurs

"primarily" by diffusion. *Endo Pharms. Inc. v. Depomed Inc.*, Case IPR2014-00656, slip op. at 9–10 (PTAB Sept. 29, 2014) (Paper 12).

Here, Patent Owner contends that the term should be construed as "rapid dissolution of the drug, followed by slow diffusion of the drug out of the water-swollen matrix, such that the drug is released at a rate controlled by the rate of diffusion." PO Resp. 16. Alternatively, Patent Owner proposes that the plain and ordinary meaning of the term is "dissolution liberates the drug molecule for release and subsequent diffusion controls the release of drug out of the matrix." *Id.* at 18. Petitioner, on the other hand, contends that our construction in the related case was correct, and that the plain and ordinary meaning of the term is "dissolution of the drug in the matrix followed by diffusion of the drug out of the matrix." Pet. Reply 2.

The main difference between the parties' constructions is whether diffusion must control the rate of release of drug out of the matrix. After considering the parties' arguments, we adopt Petitioner's construction as the broadest reasonable interpretation consistent with the Specification.

To construe the term, we start with the language of the claim. Claim 1 recites a "controlled-release oral drug dosage form" that "releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid." We determine that nothing in the claim language requires that the drug release be "at a rate controlled by the rate of diffusion," as Patent Owner asserts. To the extent Patent Owner suggests that its construction is dictated by the fact that the claim recites a "controlled-release" drug formulation for a highly soluble drug, we are not persuaded. In particular, we note that Patent Owner's own declarant,

Dr. Harold B. Hopfenberg, testified that those parameters do not necessarily require release by dissolution and diffusion:

> Q: Is it your opinion that, if you use a swellable polymer in a highly soluble drug and you get extended release that meets the requirements of Claim 1, that you must necessarily be releasing by dissolution and diffusion?
>
> A. Could you repeat that?
>
> (The record was read by the reporter.)
>
> THE WITNESS: No.

Ex. 1072, 44:17–24.

Patent Owner also argues that the Specification supports its narrowed construction. For example, Patent Owner asserts that the "focus of the '280 Patent is on slowing the rate of diffusion." PO Resp. 16. Patent Owner also notes that the Specification "states the invention disclosed 'is achieved by using a formulation in which the drug is incorporated in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the drug primarily by diffusion.'" *Id.* at 17 (quoting Ex. 1001, 5:57–62).

We are not persuaded. Our reviewing court has warned that, "[a]bsent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification or prosecution history when those sources *expressly disclaim* the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (emphasis added). Here, the Specification does not expressly disclaim other mechanisms of drug release that are not controlled by diffusion. Indeed, most of the '280 patent claims are directed to drug dosage forms that release the drug by erosion or diffusion, reciting that the dosage form "releases said drug into gastric fluid by the dissolving of said

drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix." Ex. 1001, claim 43; *see also* independent claims 19, 22, 24, 27, 28, 29, 30, 32, 33, 34, 37, 38, 39, 40, 42, 44 (reciting similar "erosion or diffusion" limitations). Thus, to the extent Patent Owner asserts those claims have sufficient written description support, the '280 patent Specification clearly is not limited to dosage forms where drug release is controlled by the rate of diffusion.

Finally, our reviewing court "counsels the PTO to avoid the temptation to limit broad claim terms solely on the basis of specification passages." *Bigio*, 381 F.3d at 1325. Accordingly, while the Specification's "Summary of the Invention" may state that the drug formulation "releases the drug primarily by diffusion" (Ex. 1001, 5:56–62), we decline to import that limitation from the Specification. *See Bigio*, 381 F.3d at 1325 (affirming Board's construction that declined to limit "hair brush" to scalp hair brushes despite statements in the "Objects of the Invention").

Patent Owner alternatively argues that a person of ordinary skill in the art would have understood the plain and ordinary meaning of claim 1 to require that "dissolution liberates the drug molecule for release and subsequent diffusion controls the release of drug out of the matrix." PO Resp. 17–18. We are not persuaded. As explained above, nothing in the claim language requires that diffusion must control the release of the drug. And, contrary to Patent Owner's suggestion, the testimony by Petitioner's declarant, Dr. Roland Bodmeier, that drug "is released by diffusion" does not amount to an admission that drug release is *controlled* by the rate of diffusion. *See id.* Rather, Dr. Bodmeier's testimony is consistent with our interpretation of the plain and ordinary meaning of the claim.

Upon considering the parties' arguments and evidence, we determine that the broadest reasonable interpretation of "releases said drug . . . by the dissolution and diffusion of said drug out of said matrix" is "releases the drug by dissolution of the drug in the matrix followed by diffusion of the drug out of the matrix."

B. Principles of Law

To prevail in its challenges to the patentability of the claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a

reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

C. The '837 Patent Is Applicable Prior Art

As an initial matter, Patent Owner asserts that the '837 patent—which is involved in every instituted ground of obviousness—is not applicable prior art to the product claims of the '280 patent.[8] PO Resp. 24. The '837 patent issued on December 10, 1996, to John W. Shell (the first-named inventor of the '280 patent), and is assigned to Patent Owner. Ex. 1010, cover page. Patent Owner argues that, as prior art under 35 U.S.C. § 102(e), the '837 patent cannot preclude patentability under 35 U.S.C. § 103(c). *Id.*

Section 103(c) states, in part:

> (1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. § 103(c)(1). Patent Owner argues that the '837 patent "fails to invalidate the Product Claims of the '280 Patent because it has the same inventor as the '280 Patent and is assigned to Patent Owner Depomed." PO Resp. 24. In its Motion to Exclude, Patent Owner further argues that

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[8] The involved product claims of the '280 patent are claims 1, 8–10, 13–15, 45, and 46. Patent Owner admits that the '837 patent constitutes prior art under 35 U.S.C. § 102(b) with respect to method claim 43. *See* Tr. 75:15–21 (agreeing the method claims are entitled to a 1999 benefit date).

because Petitioner did not assert that the '837 patent was prior art under any provision other than § 102(e) with respect to the product claims, § 103(c) acts to prevent the use of the '837 patent for showing unpatentability under § 103(a). Paper 48, 2–3.

In response, Petitioner argues that the '837 patent is also prior art under 35 U.S.C. § 102(a) because it issued before the '280 patent filing date and has different inventive entities. Pet. Reply. 2–3. Because § 103(c) does not apply to references that are § 102(a) prior art, Petitioner argues that the '837 patent is applicable prior art. *Id.*

Under § 103(c)(1), the '837 patent cannot preclude patentability unless it "qualifies as prior art *only* under one or more of subsections (e), (f), and (g) of section 102." 35 U.S.C. § 103(c)(1) (emphasis added). As noted by Petitioner, the '837 patent is also prior art under 35 U.S.C. § 102(a). Patent Owner does not dispute this. Thus, the plain language of § 103(c)(1) suggests that the '837 patent is applicable as § 102(e) prior art for purposes of obviousness. Patent Owner's complaint that the Petition did not identify the '837 patent as § 102(a) prior art is immaterial to whether the reference, in fact, qualifies as § 102(a) prior art. Petitioner's reliance on the '837 patent as §102(e) art in the Petition was sufficient to place Patent Owner on full and fair notice that Petitioner was applying the reference in the grounds. Patent Owner does not persuade us that the alleged misidentification in any way prejudiced Patent Owner's defense of its interests in this proceeding. Under these circumstances, we are not persuaded by Patent Owner's argument that we should exclude the '837 patent from the challenges asserted in this proceeding.

We now address the substantive challenges to the instituted claims.

D. The Level of Ordinary Skill in the Art

In large part, the parties agree as to the level of ordinary skill in the art. Pet. 10; PO Resp. 11. Both agree that a person of ordinary skill in the art would be a person with a Ph.D. degree in at least pharmaceutical science, chemistry, or chemical engineering along with at least two years of industry experience in the development of controlled-release oral dosage forms. Pet. 10; PO Resp. 11. Both also agree that a person of ordinary skill in the art may have an equivalent level of skill through similar education, training, and industry experience. Pet. 10; PO Resp. 11. In light of the parties' agreement, we adopt that description of the level of ordinary skill in the art for purposes of this proceeding.

E. Obviousness over Baveja, the '837 Patent, and the '548 Patent

Petitioner asserts that claims 1, 8, 9, 13–15, 45, and 46 of the '280 patent are unpatentable as obvious over Baveja, the '837 patent, and the '548 patent. Pet. 32–44; Pet. Reply 3–10. Petitioner relies on the Declaration of Dr. Bodmeier. Ex. 1016 ¶¶ 121–37. Patent Owner disagrees with Petitioner's assertions (PO Resp. 29–42), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 164–78).

1. Baveja (Ex. 1008)

Baveja discloses a dosage form comprised of a swellable hydrophilic matrix that exhibits zero-order (i.e., constant) release of a drug. Ex. 1008, Summary. Baveja uses β-adrenergic blockers propranolol hydrochloride, alprenolol hydrochloride, and metoprolol tartrate as model drugs. *Id.* at 40. Baveja describes tablets with different ratios of HPMC, sodium carboxymethylcellulose ("Na CMC"), and drug, which are then subjected to an in vitro dissolution study. The in vitro dissolution study involves placing

the tablets into a dissolution rate test apparatus with diluted HCl (pH 3.0) for three hours and then in 0.2 M phosphate buffer (pH 7.4) for another 9 hours. *Id.*

The results of the dissolution studies for tablets formed from just HPMC and drug are shown in Figures 1–3. For example, Figure 2 is reproduced below:

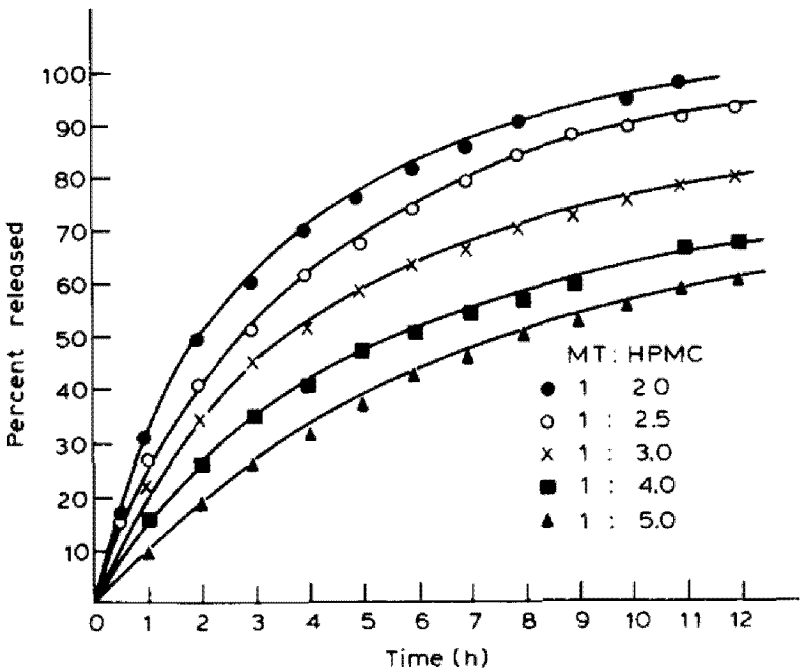

Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

Figure 2 illustrates the cumulative percent of metoprolol tartrate released as a function of time from tablets containing metoprolol tartrate and HPMC in the ratios shown. *Id.* at 41.

As explained by Baveja, the rate of release of the tablets made of drug and HPMC decreases with time, which may be due to "an increase in diffusional path length for the drug[,] which in turn may be due to slower

erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer." *Id.*

Baveja also describes tablets formed from HPMC, Na CMC, and drug in varying amounts that exhibit a nearly zero-order rate of release. *Id.*, Abstract.

2. The '837 Patent (Ex. 1010)

The '837 patent relates to the field of alkyl-substituted cellulose-based sustained-release drug dosage forms. Ex. 1010, 1:17–19. Specifically, the dosage form disclosed in the '837 patent comprises a plurality of solid particles of a drug dispersed within a non-crosslinked alkyl-substituted cellulose that "swells unrestricted dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote gastric retention of the pellets in fed-mode induced patients." *Id.* at 1:58–65. The '837 patent teaches that the particles will normally swell to a size of about 6 to 18 mm. *Id.* at 5:8–12. According to the '837 patent specification, the dosage form is particularly useful for delivering drugs in a sustained manner within the stomach. *Id.* at 2:39–43.

The '837 patent also discloses drug release experiments using drug dosage forms comprised of hydroxypropylcellulose ("HPC") and aspirin ("ASA"). *Id.* at 7:25–57. The results of the drug release experiments, which were performed in simulated gastric fluid, are shown in Figure 1, which is reproduced below.

Fig. 1

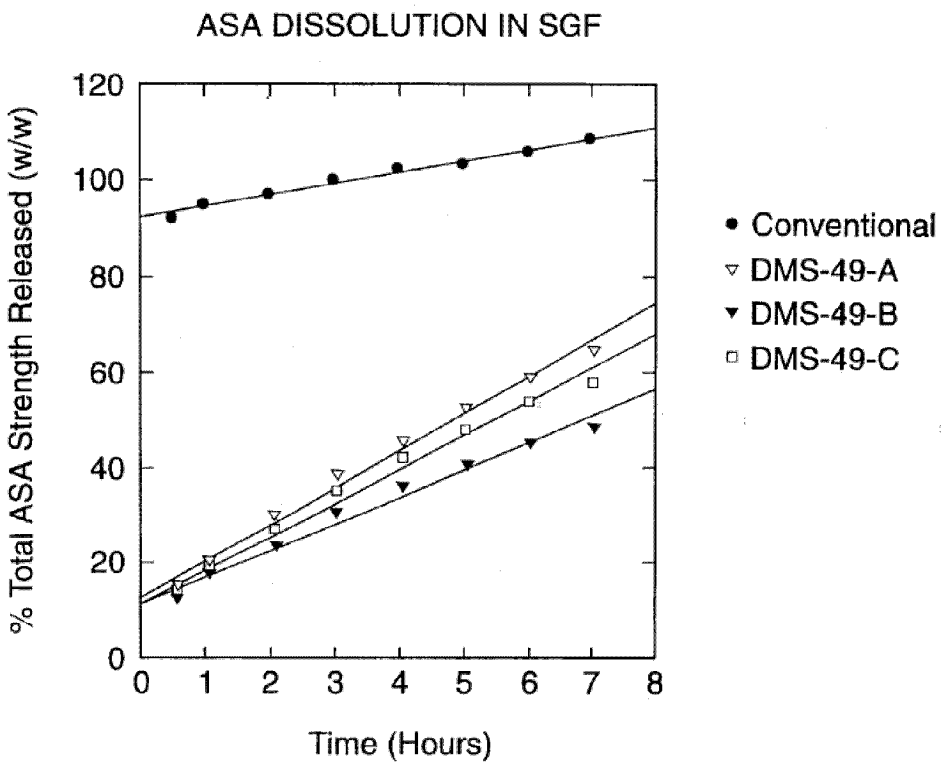

Figure 1 depicts the percentage of aspirin released over time for the various drug formulations tested, including conventional aspirin without HPC. *Id.* at 7:47–52. The release of aspirin was measured at various intervals up to seven hours. *Id.*

3. The '548 Patent (Ex. 1017)

The '548 patent issued on October 3, 1989, and relates to a controlled-release dosage form comprising a drug and at least two different cellulose ethers. Ex. 1017, 1:12–16. According to the '548 patent specification, "[an] object of the present invention is to provide a dosage form of delivering a drug in the gastrointestinal tract that substantially avoids a premature disintegration." *Id.* at 3:1–4. The '548 patent specification also states that the disclosed invention "delivers a drug at a rate of dosage form release that

corresponds to the rate of change of the integrity of the dosage form over a prolonged period of at least eight hours." *Id.* at 3:4–7.

Moreover, the dosage form uses cellulose ethers, which swell extensively when hydrated and lessens direct drug contact with mucosal tissues. *Id.* at 11:23–26. The drug delivery matrix is suitable for gastric retention over the releasing lifetime of the dosage system. *Id.* at 10:65–68. Furthermore, "when all the drug is released, the system bioerodes into innocuous particles and dissolved polymers that pass from the gastrointestinal tract." *Id.* at 10:68–11:3.

4. Analysis

Petitioner asserts that claims 1, 8, 9, 13–15, 45, and 46 of the '280 patent are unpatentable as obvious over Baveja, the '837 patent, and the '548 patent. We have reviewed the arguments and evidence presented by both parties, and we are not persuaded that Petitioner has shown by a preponderance of the evidence that the claims would have been obvious over the cited references.

Petitioner argues that "[t]he only difference between the disclosure in Baveja and claim 1, is that Baveja does not expressly disclose certain inherent properties and release characteristics of its formulations." Pet. 32–33. Specifically, Petitioner asserts that two limitations of claim 1 are disclosed inherently, not expressly, in Baveja: (1) "dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode" (i.e., the "swelling" limitation) (Pet. 35–36); and (2) "remains substantially intact

until substantially all of said drug is released" (i.e., the "substantially intact" limitation) (*id.* at 36).

Looking first at the limitations that Petitioner contends are expressly disclosed, Patent Owner disagrees with Petitioner's contentions, arguing that Baveja also does not disclose, either expressly or inherently, drug release by "dissolution and diffusion." PO Resp. 30–32. Indeed, Patent Owner contends that Baveja actually teaches away from drug release by dissolution and diffusion because it describes the dosage form relied upon by Petitioner as having a "major disadvantage" because it does not exhibit zero-order release. *Id.* (citing Ex. 1008, 40). We find, however, that Baveja teaches "dissolution and diffusion" expressly when it states that "Figs. 1–3 reveal that the rate of release decreased with time and this may be due to an increase in diffusional path length for the drug which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer." Ex. 1008, 41. Moreover, the fact that Baveja may prefer dosage forms that exhibit zero-order release, over those that do not, does not teach away from the claimed invention. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("This court has further explained that just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

For the remaining limitations of claim 1 that Petitioner contends are expressly disclosed, based on the evidence presented, we are persuaded that Petitioner has established that Baveja teaches those limitations expressly. Pet. 16–18; Ex. 1016 ¶¶ 74–76, 83–86. We further agree with Petitioner that Baveja does not expressly disclose the "swelling" limitation and the "substantially intact" limitation. *See* Pet. 16–18.

Petitioner, however, asserts that Baveja inherently teaches the "swelling" and "substantially intact" limitations. Pet. 35–36. To prove inherency, Petitioner must establish that "the missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). We are not persuaded that Petitioner has met this test for either limitation.

Regarding the "swelling" limitation, Petitioner asserts that Baveja discloses a tablet that is 11 mm in diameter prior to imbibition of water and contains 25% alprenolol HCl and 75% HPMC. Pet. 16–17 (citing Ex. 1016 ¶ 78); *see* Ex. 1008, Fig. 1. Petitioner concludes that Baveja inherently discloses a dosage form that swells in a dimensionally unrestricted manner to a size exceeding the pyloric diameter and that will promote retention in the stomach during the fed mode. Pet. 35 (citing Ex. 1016 ¶ 123). Petitioner bases its argument in part on the '280 patent Specification's disclosure that "[p]articles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours." Ex. 1001, 12:1–3. Although Baveja does disclose a "swelling front" (Ex. 1008, 41), we are not persuaded that Petitioner has shown sufficiently that Baveja inherently teaches the entirety of the "swelling" limitation. Specifically, we are not persuaded that Petitioner has shown that Baveja necessarily teaches swelling in a "dimensionally unrestricted manner to a size exceeding the pyloric diameter" or that "will promote retention in the stomach during the fed mode." PO Resp. 37–39. As Patent Owner asserts, Baveja discloses only a single dimension of the dosage form—the diameter—and is silent as to the thickness of the dosage form. *Id.* at 37; Ex. 2010 ¶ 111.

As for the "substantially intact" limitation, Petitioner argues that Baveja's formulation would inherently remain substantially intact. Pet. 36. As support, Petitioner relies on both the testimony of Dr. Bodmeier and the test results of Dr. Kinam Park. *Id.* According to Petitioner, Dr. Park re-created two formulations in Baveja to determine the release kinetics and swelling properties of the dosage forms. Pet. 19. As explained in our Decision to Institute, however, because Dr. Park did not provide evidence of a positive control, we cannot conclude with sufficient certainty that Dr. Park's dosage forms were, in fact, the same dosage forms disclosed by Baveja. Dec. Inst. 11. During oral argument, Petitioner accepted our finding. Tr. 29:21–22 ("We accept the Board's conclusion regarding the prior test results . . . ."). And, as explained in our Decision to Institute, we do not give persuasive weight to Dr. Bodmeier's unsupported opinion that the Baveja tablets will remain substantially intact. Dec. Inst. 11–12. Accordingly, we are not persuaded that Baveja inherently teaches the "substantially intact" limitation.

Petitioner provides, however, alternative sources for teaching these two limitations missing from Baveja. First, Petitioner asserts that the '837 patent discloses expressly the "swelling" and "substantially intact" limitations. Pet. 37–38. We agree. The '837 patent discloses that the dosage form "swells unrestricted dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote gastric retention of the pellets in fed-mode induced patients." Ex. 1010, 1:62–66. The '837 patent also discloses that the drugs are dispersed in the "selected alkyl-substituted cellulose such as hydroxyethylcellulose or hydroxy propylcellulose," and that "because these polymers dissolve very slowly in

gastric fluid, the particles maintain their integrity over at least a substantial portion (i.e., at least about 90% and preferably over 100% of the intended dosing period)." *Id.* at 4:31–46.

Second, Petitioner asserts that the '548 patent teaches the "swelling" and "substantially intact" limitations. Pet. 41. We are not persuaded, however, that the cited portions of the '548 patent teach or suggest either of these limitations. For example, as Patent Owner notes (PO Resp. 39), Petitioner points to nothing in the '548 patent that suggests the dosage form swells in a "dimensionally unrestricted manner" to a size exceeding the pyloric diameter "in fed mode," as required by the "swelling" limitation. Nor are we persuaded that the '548 patent's teaching that the dosage form "exhibit[s] better mechanical integrity" teaches or suggests a dosage form that remains "substantially intact," as defined by the Specification, particularly in light of the '548 patent's disclosure of drug release by erosion. *See* Ex. 1017, 3:1–7 (describing drug release at a rate that "corresponds to the rate of change of the integrity of the dosage form over a prolonged period of at least eight hours").

Notwithstanding our findings with respect to the '548 patent, we are persuaded that Petitioner has established that each limitation of claim 1 was known in the art, as evidenced by the teachings of Baveja and the '837 patent. A patent, however, "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Petitioner must also show that there was a reason to combine those elements to achieve the claimed invention with a reasonable expectation of success. *See PAR Pharm.*, 773 F.3d at 1193. To make that determination, we can look to "interrelated teachings of multiple patents; the

effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art." *Id.* We can also look to the nature of the problem to be solved. *In re Gartside*, 203 F.3d 1305, 1319 (Fed. Cir. 2000) (holding that suggestion to combine "may come from, *inter alia*, the teachings of the references themselves and, in some cases, from the nature of the problem to be solved"). After considering the parties' arguments and evidence, however, we are not persuaded that Petitioner has made a sufficient showing that a person of ordinary skill would have combined the teachings in the manner contended by Petitioner.

Petitioner argues that a person of ordinary skill in the art would have been led to combine the teachings of Baveja and the '837 patent for several reasons.[9] Pet. 38 (citing Ex. 1016 ¶¶127, 131). First, Petitioner argues that the references have interrelated teachings. According to Petitioner, both references are directed to controlled-release dosage forms that contain HPMC with similar drug-to-polymer weight ratios. *Id.*; Ex. 1016 ¶ 127. For example, claim 1 of the '837 patent recites a drug to polymer ratio of about 1:9 to 9:1. Ex. 1010, claim 1. Baveja's matrix contains a drug-to-polymer ratio that falls within the weight ratio range claimed by the '837 patent. Pet. 38 (citing Ex. 1008, Figs. 1 and 2); Ex. 1016 ¶ 127. Moreover, Petitioner argues that both references teach drug formulations for high

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[9] Petitioner also argues that a person of ordinary skill in the art would have been motivated to combine Baveja and the '548 patent to achieve the claimed invention. Pet. 41–42. Because we are not persuaded that the '548 patent teaches the "swelling" and "substantially intact" limitations, we do not address further the proposed combination of Baveja and the '548 patent.

solubility drugs. Pet. 38; Ex. 1016 ¶ 128. Petitioner and its declarant, Dr. Bodmeier, assert also that "the advantages of formulations retained in the stomach and techniques for creating swellable polymer formulations retained in the stomach, were well known by a [person of ordinary skill in the art]." Pet. 36; Ex. 1016 ¶¶ 123, 51–57. Petitioner then concludes that "it would be natural for a POSA to combine the teachings of these two references to arrive at the formulation in claim 1 of the '280 patent." Pet. 39; Ex. 1016 ¶ 128.

Second, Petitioner argues that a person of ordinary skill in the art would have a reason to combine Baveja and the '837 patent given the nature of the problem to be solved: "to formulate a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." Pet. 41 (citing Ex. 1016 ¶ 131). As such, Petitioner argues that a person of ordinary skill in the art reading Baveja would look to the '837 patent "to confirm that the same polymer will in fact be retained in the stomach and remain substantially intact." *Id.* (citing Ex. 1016 ¶ 131).

In response, Patent Owner argues that Petitioner has failed to demonstrate a motivation to combine the cited references with a reasonable expectation of success. Patent Owner challenges Dr. Bodmeier's statement that it would be "natural" to combine Baveja and the '837 patent. PO Resp. 40. According to Patent Owner, Dr. Bodmeier fails to provide any substantive evidence to support his testimony that it would take him "a week" to come up with the claimed invention. *Id.* at 41 (quoting Ex. 2018, 80:19–81:8). In contrast to Dr. Bodmeier's testimony, Patent Owner notes

that Jenny-Louie Helm, an inventor of the '280 patent ("Inventor Helm"), testified that it "took years of research and testing in the laboratory to manipulate different variables, such as type of polymer, molecular weight, particle size, dosage size, matrix chemical structure, and manufacturing processes, to come up with the claimed inventions." *Id.*; Ex. 2016 ¶ 21 (Helm Decl.) ("It took me three years testing various polymers with guidance of Dr. Shell to achieve the Captopril formulation that contained the aspects of the claims of the '475 and '280 Patents."). Consistent with Inventor Helm's testimony, Patent Owner asserts that its declarant, Dr. Hopfenberg, testified that a person of ordinary skill in the art would not have reasonably expected to successfully achieve the claimed invention given that a "vast array of structural considerations affect polymer and matrix properties." PO Resp. 42 (citing Ex. 2010 ¶ 59).

On the record developed at trial, we are not persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reason to combine the references with a reasonable expectation of success. Although the references may have interrelated teachings, as Petitioner asserts, Petitioner has not explained persuasively *how or why* a person of ordinary skill in the art would have combined the "swelling" and "substantially intact" features of the '837 patent formulation with the formulation of Baveja.

In its Reply, Petitioner asserted another reason to combine the cited references:

> A [person of ordinary skill in the art] would look to (1) Baveja to learn how to adjust the rate of high solubility drug release by varying the drug-to-polymer (HPMC) weight ratio and (2) either the '837 or the '548 patent to confirm that the same type

> of polymer used in Baveja will (a) swell in a dimensionally unrestricted manner to a size exceeding the pyloric diameter, (b) be retained in the stomach during the fed mode, and (c) remain substantially intact until all of the drug is released.

Pet. Reply 8–9; Ex. 1016 ¶¶ 122–36. But here, again, Petitioner speaks in generalizations and does not explain persuasively *why* a person of ordinary skill in the art, learning from Baveja how to adjust the rate of drug release by varying the drug-to-polymer weight ratio, would need or want to look to the '837 patent to "confirm" the "swelling" and "substantially intact" properties. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing district court's judgment of invalidity where expert's testimony "was vague and did not articulate reasons why a person of ordinary skill in the art at the time of the invention would combine these references").

To the extent Petitioner relies on the nature of the problem to be solved to supply the reason for the combination, we remain unpersuaded. Petitioner's recitation of the nature of the problem to be solved is essentially a recitation of claim 1 itself: "to formulate a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." Pet. 41. As our reviewing court has recently reminded us, however, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)). As such, the Federal Circuit stated that when considering the reason to combine, "the problem examined is not the

specific problem solved by the invention." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Here, the claim represents the specific problem solved by the invention, rather than the general problem facing the inventors. Thus, we find that by defining the nature of the problem to be solved as the specific problem solved by the invention, Petitioner has relied on impermissible hindsight to supply the reason to combine Baveja and the '837 patent. *Id.* (affirming the district court's recognition that "an overly narrow 'statement of the problem [can] represent[] a form of prohibited reliance on hindsight, [because] [o]ften the inventive contribution lies in defining the problem in a new revelatory way'") (quoting *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (alterations in original)).

Even if we were to find that Petitioner has established that a person of ordinary skill in the art would have had a reason to combine the teachings of Baveja and the '837 patent, we are still not persuaded that Petitioner has established that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

Petitioner argues that, at the time of the invention, a person of ordinary skill in the art "understood how to achieve" the claimed drug formulation. Pet. 36–37. For example, Petitioner and its declarant argue that a person of ordinary skill in the art would have known "techniques for creating swellable polymer formulations retained in the stomach." Pet. 35–36; Ex. 1016 ¶¶ 51–57, 123. Petitioner also argues that a person of ordinary skill in the art would have known how to construct a matrix that would remain intact because it was well known that "increasing the viscosity of HPMC (based on grade) or the concentration (by altering the drug-to-polymer weight ratio) strengthens the matrix, resulting in a dosage form that

would remain physically intact over the dosing period." Pet. 36–37; Ex. 1016 ¶¶ 61– 65, 125.

We are not persuaded that a person of ordinary skill in the art would have had a reasonable expectation of success, in part, because both parties' declarants testified about the number of formulation considerations at play when preparing a drug formulation. For example, Petitioner's declarant testified that there were formulation considerations such as "molecular weight, chemical substitution, particle size, hydration rate effect, polymer content, dosage form, dosage size and manufacturing processes." Ex. 1016 ¶ 41. Similarly, Patent Owner's declarant stated that "[a] person of ordinary skill in the art understands that formulation of a polymer matrix involves a vast array of interacting 'formulation considerations' affecting polymer and matrix properties." Ex. 2010 ¶ 161. Despite this testimony from its own declarant (as confirmed by Patent Owner's declarant), we find that Petitioner does not address sufficiently why a person of ordinary skill in the art would believe it could modify the formulation of Baveja to incorporate the "swelling" and "substantially intact" features of the '837 patent without, for example, affecting the other desired properties of the original Baveja formulation (e.g., the drug release profile). Petitioner has not identified any combinations of Baveja and the '837 patent that would be most promising to try. As such, we reach the same conclusion as the Federal Circuit in *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013). That is, we find that, "[w]ithout a reasonable expectation of success or clues pointing to the most promising combinations, an artisan could have spent year experimenting without success." *Id.*

Finally, during cross-examination, Dr. Bodmeier testified that it would take him "within a week" to come up with the claimed formulations. *See* PO Resp. 41; Ex. 2018, 80:19–81:8. In its Reply, Petitioner also argues that "[e]ven if the Board accepts that Dr. Park's tablets are not identical to Baveja's tablets, Baveja's disclosures led Dr. Park to create dosage forms that fall within the scope of claim 1 using techniques well-known to a POSA, . . . confirming that the claims are obvious over Baveja." Pet. Reply 5.

The problem with both Dr. Bodmeier's testimony and Dr. Park's test results is that neither testified from the perspective of a person of ordinary skill in the art *at the time of the invention*. Specifically, Dr. Bodmeier's testimony was as follows:

> Q. Could you give me an estimate on how long in the lab it would take you, a day, two weeks of experimentation to come up with the formulations of the '280 patent?
>
> A. Yes. Obviously compare to other patents, you know, this is not a claim to a specific drug, you know. It's to a drug class. So I think to develop a gastro retentive system which is mechanically stable and has release profiles, for example, shown in the examples or in Baveja, I think you can do that within a week.

Ex. 2018, 80:19–81:8.

And Dr. Park attested that, "[i]n performing the testing set forth in this Declaration, [he] considered and relied upon [his] education, background, and years of experience in the field of pharmaceutical sciences." Ex. 1020 ¶ 13. Thus, even if we did accept Dr. Bodmeier and Dr. Park's testimony as true, both are irrelevant to our obviousness analysis. *InTouch Techs.*, 751 F.3d at 1352 (stating expert's testimony as to what a skilled artisan could

accomplish at the time the testimony was given "is not the relevant inquiry" to what a skilled artisan would have understood as of the time of the invention).

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 8, 9, 13–15, 45, and 46 are unpatentable as obvious over Baveja, the '837 patent, and the '548 patent.

F. Obviousness of Claim 10 over Baveja, Kim, the '837 Patent, and the '548 Patent

Petitioner asserts that claim 10 of the '280 patent is unpatentable as obvious over Baveja, Kim, the '837 patent, and the '548 patent, relying on the Declaration of Dr. Bodmeier. Pet. 44–47; Pet. Reply 10; Ex. 1016 ¶¶ 158–63. Patent Owner disagrees with Petitioner's assertions (PO Resp. 42–44), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 179–87).

1. Kim (Ex. 1019)

Kim discusses drug release from compressed tablets manufactured with a powder mixture of poly(ethylene oxide) ("PEO"), a drug, and magnesium stearate. Ex. 1019, 303. In one example, Kim describes a dosage form wherein the PEO has an average molecular weight of 4,000,000. *Id.*

2. Analysis

Claim 10 of the '280 patent depends from claim 1 and further requires a polymeric matrix formed of PEO at a molecular weight of at least about 4,000,000. Ex. 1001, claim 10. As determined above, we find that the combination of Baveja and the '837 patent teaches each limitation of

claim 1. We also find that Kim teaches the additional limitation of claim 10, which Patent Owner does not dispute. PO Resp. 42–44.

Because claim 10 depends from claim 1, we determine, for the same reasons stated above, that Petitioner has failed to establish that a person of ordinary skill in the art would have had a reason to combine the teachings of Baveja, the '837 patent, and Kim to achieve the claimed invention with a reasonable expectation of success.

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claim 10 is unpatentable as obvious over Baveja, Kim, and the '837 patent.

G. Obviousness over Baveja, the '837 Patent, and Colombo

Petitioner asserts that claim 43 of the '280 patent is unpatentable as obvious over Baveja, the '837 patent, and Colombo, relying on the Declaration of Dr. Bodmeier. Pet. 58–60; Pet. Reply 10–13; Ex. 1016 ¶¶ 188–97. Patent Owner disagrees with Petitioner's assertions (PO Resp. 44–49), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 188–99).

1. Colombo (Ex. 1009)

Colombo relates to swellable matrix systems in the form of a tablet comprising a mixture of the drug diltiazem, HPMC, ethylcellulose, and mannitol. Ex. 1009, 44. Colombo discloses three different matrices: Case 0, the plain matrix; Case 1, the matrix coated with cellulose acetate propionate ("CAP") on one face; and Case 2, the matrix coated with CAP on both faces. *Id.* Colombo describes "[s]welling and release experiments" in which the matrices were swollen in deionized water for 120 minutes, and the

drug release measurements were obtained concomitantly with the matrix swelling observations. *Id.*

Colombo describes and depicts the morphological changes in the matrices over time, observing that, in the uncoated system (Case 0), "[v]ery quickly (after 15 min) the swelling of the matrix moves both in axial and radial directions." *Id.* Colombo also discloses the drug release profiles of the systems. *Id.* at 45. Figure 5 of Colombo is reproduced below:

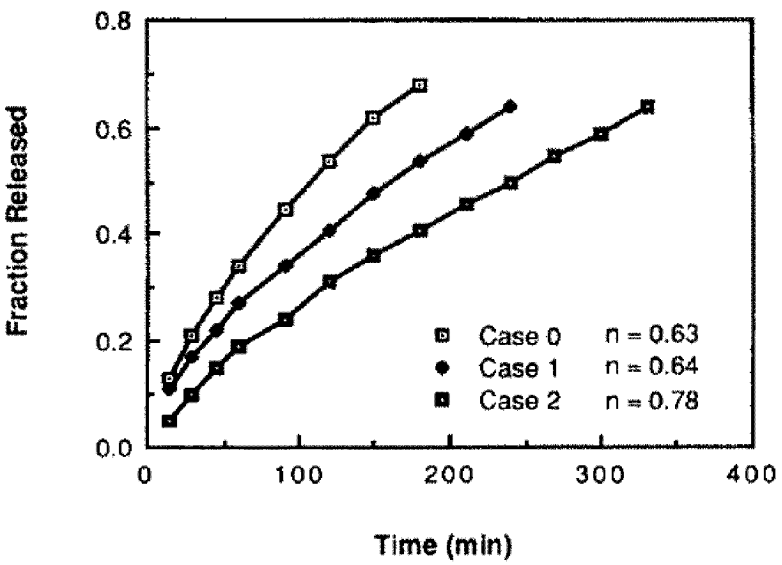

Fig. 5. Drug release profiles of the systems. Calculated values of exponent *n* of Eqn 2 are also shown.

Figure 5 depicts the fraction of diltiazem released over time for the Case 0, Case 1, and Case 2 matrices.

2. Analysis

Petitioner asserts that the subject matter of claim 43 of the '280 patent would have been obvious over the teachings of Baveja, the '837 patent, and Colombo. Pet. 58–60. Petitioner argues that Colombo and Baveja each "disclose the limitations set forth in claim 43, except for the method of administration, which is expressly disclosed by the '837 patent." *Id.* at 58. Petitioner further contends that a person of ordinary skill in the art would

have been motivated to combine the teachings of the '837 patent with Baveja and Colombo given the nature of the problem to be solved (identified above) and the interrelated teachings of the art. *Id.* at 58–59.

As explained above, we are not persuaded that Baveja teaches inherently the "swelling" limitation. Similarly, we are not persuaded that Colombo teaches this limitation, either. Colombo teaches studies in which the matrices were swollen in deionized *water*. Ex. 1009, 44. Petitioner directs us to no persuasive evidence that Columbo's matrices swell by "imbibition of *gastric fluid*," as required by the claims. That is, Petitioner has not established that deionized water is an "artificial fluid[] recognized by those skilled in the art as a suitable model for the fluid of the human stomach," as required by our construction of "gastric fluid." Thus, we are not persuaded that Colombo teaches the "swelling" limitation, either expressly or inherently.

We are also not persuaded that Colombo teaches "releas[ing] substantially all of said drug within about ten hours after such immersion." Figure 5 of Colombo does not show any formulation that ever releases at least 80% of the drug, as required by the claims. Ex. 1009, Fig. 5.

Nevertheless, we are persuaded that Petitioner has established that each limitation of claim 43 was known in the art, as evidenced by the teachings of Baveja, the '837 patent, and Colombo. For the same reasons stated above with respect to claim 1, however, we find that Petitioner has not shown sufficiently that a person of ordinary skill in the art would have had a reason to combine the references to achieve the claimed invention with a reasonable expectation of success. Once again, Petitioner frames the nature of the problem to be solved too narrowly, indicating a hindsight bias. *See*

Insite Vision, 783 F.3d at 859. Moreover, as Patent Owner argues, Petitioner "fails to prove that coming up with the invention of Claim 43 by combination of prior art references took just routine experimentation by one of skill in the art." PO Resp. 49. We find that Petitioner does not explain persuasively why a person of ordinary skill in the art would have had a reasonable expectation of success beyond just the knowledge that each limitation of the claim was known in the art at the time of the invention.

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claim 43 is unpatentable as obvious over Baveja, the '837 patent, and Colombo.

H. Secondary Considerations of Nonobviousness

In light of our determination that Petitioner has not shown by a preponderance of the evidence that any of the challenged claims are unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

III. MOTIONS TO EXCLUDE EVIDENCE

Both parties filed motions to exclude evidence offered by the other side. The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence ("FRE"). *See* 37 C.F.R. §§ 42.20(c), 42.62(a). We address each party's motion in turn.

1. Petitioner's Motion to Exclude Evidence

Petitioner moves to exclude portions of Dr. Hopfenberg's declaration and a claim chart for Gralise® (Ex. 2013) as improperly incorporated by reference and as irrelevant because they are improperly incorporated.

Paper 41, 3–6. We decline to do so. As explained in our prior Order (Paper 30), to the extent any such violations have occurred, we have not considered such evidence in reaching our decision. Therefore, we dismiss Petitioner's motion as moot.

Petitioner also moves to exclude certain testimony of Inventor Helm. Paper 41, 10–13. We decline to do so. To the extent we have relied on the testimony of Inventor Helm, that testimony was based on her own work. *See* Ex. 2016 ¶ 21 (testifying how long it took her to develop an embodiment of the claims). Such testimony based on her own personal knowledge is relevant and proper lay witness testimony under FRE 701, 602, and 401/402/403. Accordingly, we deny Petitioner's motion as to this evidence.

Petitioner also moves to exclude certain evidence relating to Patent Owner's assertions of commercial success, licensing, long-felt but unmet need, and unexpected results. Paper 41, 6–15. Given our determination that we need not reach Patent Owner's evidence of secondary considerations, we need not reach the merits of Petitioner's Motion to Exclude and dismiss the motion as moot.

2. Patent Owner's Motion to Exclude Evidence

Patent Owner moves to exclude the '837 patent as irrelevant to the product claims in this proceeding because it allegedly does not constitute prior art. Paper 48, 1–3. We have addressed this argument and deny Patent Owner's motion to exclude the '837 patent for the reasons stated above.

Patent Owner also moves to exclude (1) Exhibits 1022, 1023, 1062, and 1063 (*id.* at 3–7); (2) Exhibit 1071 and the related testimony of Dr. Bodmeier (*id.* at 11–13); and (3) portions of the cross-examination testimony of Dr. Eric Gaier (*id.* at 13–16). Because we did not rely on any

of these exhibits or testimony in reaching our Decision here, we dismiss Patent Owner's motion to exclude this evidence as moot.

IV. CONCLUSION

We conclude that Petitioner has not shown by a preponderance of the evidence that claims 1, 8–10, 13–15, 43, 45, and 46 of the '280 patent are unpatentable under 35 US.C. § 103.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 8–10, 13–15, 43, 45, and 46 of the '280 patent are not held unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is *denied in part and otherwise dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *denied in part and otherwise dismissed*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2014-00377
Patent 6,635,280 B2

PETITIONER:

Gasper J. LaRosa
gjlarosa@jonesday.com

Kelsey I. Nix
knix@jonesday.com

Lynda Q. Nguyen
lqnguyen@jonesday.com

PATENT OWNER:

Judy M. Mohr
JMohr@MWE.com

Paul Andre
PAndre@kramerlevin.com

Geoffrey G. Hu
GHu@kramerlevin.com

Trials@uspto.gov
571-272-7822

Paper 73
Entered: July 8, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PURDUE PHARMA L.P.,
Petitioner,

v.

DEPOMED, INC.,
Patent Owner.

Case IPR2014-00378
Patent 6,340,475 B2

Before ERICA A. FRANKLIN, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Purdue Pharma L.P. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 8–15, 61, and 62 of U.S. Patent No. 6,340,475 B2 (Ex. 1001, "the '475 patent"). Paper 1 ("Pet."). Depomed, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp."). On July 10, 2014, we instituted an *inter partes* review of claims 1, 8–10, 13–15, 61, and 62 on certain grounds of unpatentability alleged in the Petition. Paper 10 ("Dec. Inst."), 25. Patent Owner timely filed a Response (Paper 25, "PO Resp."), to which Petitioner timely filed a Reply (Paper 36, "Pet. Reply").

Both parties filed motions to exclude certain exhibits and testimony. Paper 42 (Petitioner); Paper 49 (Patent Owner). Both parties opposed the other's motion to exclude. Paper 57 (Patent Owner Opposition); Paper 52 (Petitioner Opposition). And both parties filed reply briefs in support of their motions to exclude. Paper 59 (Petitioner Reply); Paper 62 (Patent Owner Reply).

Patent Owner also filed a Motion for Observation (Paper 47) on certain cross-examination testimony of Petitioner's declarant Dr. Eric M. Gaier, and Petitioner filed a Response (Paper 53).

A consolidated oral hearing for this proceeding and Cases IPR2014-00377 and IPR2014-00379 was held on March 19, 2015, a transcript of which has been entered in the record.[1] Paper 72 ("Tr.")

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[1] Petitioner and Patent Owner filed Objections to Demonstrative Exhibits. Paper 67 (Patent Owner); Paper 68 (Petitioner). In this Final Written Decision, we rely directly on the arguments presented properly in the

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 8–10, 13–15, 61, and 62 of the '475 patent are unpatentable.[2]

A. Related Proceedings

Petitioner and Patent Owner identify various district court actions involving the '475 patent, including an action involving the parties titled *Depomed, Inc. v. Purdue Pharma L.P.*, No. 3:13-00571 (D.N.J.). Pet. ix; Paper 5, 2–3.

Petitioner has also filed two related petitions for *inter partes* review. One petition involves U.S. Patent No. 6,635,280 B2, which is a continuation of the '475 patent. *See* IPR2014-00377. The other petition involves the '475 patent, as well, but challenges different claims. *See* IPR2014-00379. We issue Final Written Decisions in those two related proceedings concurrently herewith.

B. The '475 Patent (Ex. 1001)

The '475 patent relates to drugs formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic

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parties' briefs and the evidence of record. The demonstrative exhibits were only considered to the extent they are consistent with those arguments and evidence.

[2] On February 20, 2015, Patent Owner objected to Petitioner's use of a condensed font in Petitioner's Reply paper. Petitioner, however, appears to have used the same condensed font throughout this proceeding. *Compare* Pet. *with* Pet. Reply (using same font). In light of Patent Owner's late objection, we deem the objection to be waived.

polymers that swell upon imbibition of water to a size large enough to promote gastric retention of the drug during the fed mode. Ex. 1001, Abstract. Drugs administered by conventional tablets generally become available to body fluids at a high rate initially, followed by a rapid decline. *Id.* at 1:31–33. To address that issue, controlled drug delivery systems were introduced in the 1970's. *Id.* at 1:35–37. Many of the controlled delivery systems utilize hydrophilic, polymeric matrices that provide controlled release of sparingly soluble drugs. For soluble drugs, however, such matrices do not provide adequate control of drug release. *Id.* at 1:45–50.

The claimed invention allows drugs that are highly soluble in water to be administered orally in a way that will prolong their release rate throughout the duration of the fed mode. *Id.* at 5:32–36. This prolonged release rate reduces the problem of transient overdosing, and controls the dosage to safer and more effective levels over an extended period of time. *Id.* at 5:36–41. Moreover, particles exceeding about 1 cm in size are larger than the pylorus and are retained in the stomach for approximately 4 to 6 hours. *Id.* at 11:66–12:2. The Specification states that these benefits are due, in part, to using a polymeric matrix that is water-swellable rather than just hydrophilic, that has an erosion rate substantially slower than its swelling rate, and that releases the drug primarily by diffusion rather than erosion. *Id.* at 5:57–62. Preferred polymeric matrices include water-swellable polymers such as hydroxypropylmethylcellulose ("HPMC") and poly(ethylene) oxide ("PEO"). *Id.* at 7:54–8:51.

C. Illustrative Claim

Claim 1 is illustrative and is reproduced below:

> 1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug within about eight hours after such immersion, and that remains substantially intact until all of said drug is released.

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

Claims	**Basis**	**References**
1, 8, 9, 13–15, and 61	§ 103	Baveja,[3] the '837 patent,[4] and the '548 patent[5]
10	§ 103	Baveja, Kim,[6] the '837 patent, and the '548 patent

[3] Baveja et al., *Zero-Order Release Hydrophilic Matrix Tablets of β-adrenergic Blockers*, 39 INT'L J. OF PHARM. 39–45 (1987) (Ex. 1005).
[4] John W. Shell, US 5,582,837, issued Dec. 10, 1996 (Ex. 1010).
[5] Edgren et al., US 4,871,548, issued Oct. 3, 1989 (Ex. 1011).
[6] Cherng-ju Kim, *Drug Release from Compressed Hydrophilic POLYOX-WSR Tablets*, 84 J. PHARM. SCIENCES 303–306 (1995) (Ex. 10129).

Claims	Basis	References
1, 8, 9, 13, 14, 61, and 62	§ 103	Colombo,[7] the '837 patent, and the '548 patent

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279–81 (Fed. Cir. 2015). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

[7] Colombo et al., *Drug Release Modulation by Physical Restrictions of Matrix Swelling*, 63 INT'L J. OF PHARM. 43–48 (1990) (EX. 1006).

1. Prior Construed Claim Terms

We construed the following claim terms in the Decision to Institute.

Claim Term	Claim	Construction
"gastric fluid"	1	"[b]oth the fluid in the stomach and simulated or artificial fluids recognized by those skilled in the art as a suitable model for the fluid of the human stomach" (Dec. Inst. 6)
"releases substantially all of said drug within about eight hours after such immersion"	1	"[a]t least 80% of the drug has been released after eight hours of immersion in gastric fluid" (Dec. Inst. 6)
"substantially intact"	1	"a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles" (Dec. Inst. 7)

Because nothing in the full record developed during trial persuades us to deviate from our prior constructions, we adopt those constructions for purposes of this Decision.

Patent Owner requests construction of two additional terms, which we address below.

2. "until all of said drug is released"

Claim 1 recites the phrase "remains substantially intact until all of said drug is released." We have construed the term "substantially intact," but Patent Owner also requests construction of the phrase "until all of said drug is released." Patent Owner asserts that the phrase should be construed

to mean "until the plateau of the dissolution profile characterizing drug release from the swollen dosage form is reached." PO Resp. 14. Petitioner does not challenge Patent Owner's construction in its Reply.

Patent Owner argues that the '475 Specification discloses drug release profiles that "show a release plateau for metformin from the dosage forms of the invention that typically does not reach 100%." *Id.* (citing Ex. 1001, Fig. 1). Patent Owner also relies on the FDA guidance documents that state a dissolution assay should be run until "either 80% of the drug from the drug product is released or an asymptote is reached." *Id.* at 15 (quoting Ex. 2009, 6) (emphasis omitted). Finally, Patent Owner asserts that its declarant, Dr. Harold B. Hopfenberg agrees with its construction. *Id.* (citing Ex. 2010 ¶ 54).

We are not persuaded by Patent Owner's arguments. The plain meaning of "until *all* of said drug is released" is evident. If we were to adopt Patent Owner's argument that "all" can mean "less than all," we would be ignoring the plain meaning of the term. Moreover, although Patent Owner is correct that certain embodiments in the Specification plateau at less than 100% of drug release, we note that certain other embodiments do plateau at 100%. *See* Ex. 1001, Fig. 1 (curve marked by filled diamonds); *see also August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1285 (Fed. Cir. 2011) ("The mere fact that there is an alternative embodiment disclosed in the [asserted patent] that is not encompassed by [our] claim construction does not outweigh the language of the claim, especially when [our] construction is supported by the intrinsic evidence.") (citation omitted).

Furthermore, as noted above, we have determined that, as properly construed, the phrase "releases substantially all" in claim 1 means "at least

80% of the drug has been released." If we were to interpret "all" to mean the point at which the drug release profile plateaus—even if less than 80%—then it would be possible for a dosage form to release "all" of a drug, but not "substantially all" of the drug. Such an inconsistency within the claim would not be a reasonable construction of the term "all." Accordingly, we decline to construe "until all of said drug is released" as broadly as Patent Owner requests and, instead, construe it according to its plain, ordinary meaning.

3. "releases said drug . . . by the dissolution and diffusion of said drug out of said matrix"

The parties dispute the construction of the term "releases said drug . . . by the dissolution and diffusion of said drug out of said matrix" (i.e., the "dissolution and diffusion" limitation) in claim 1. We did not construe this term in the Decision to Institute for this proceeding. As Petitioner notes, however, we construed this term in related case IPR2014-00654, which also involves the '475 patent. Pet. Reply 1. In the Decision to Institute in that case, we preliminarily construed the term according to its plain and ordinary meaning and declined to limit claim 1 to require that drug release occurs "primarily" by diffusion. *Endo Pharms. Inc. v. Depomed Inc.*, Case IPR2014-00654, slip op. at 7–8 (PTAB Sept. 29, 2014) (Paper 12).

Here, Patent Owner contends that the term should be construed as "rapid dissolution of the drug, followed by slow diffusion of the drug out of the water-swollen matrix, such that the drug is released at a rate controlled by the rate of diffusion." PO Resp. 16. Alternatively, Patent Owner proposes that the plain and ordinary meaning of the term is "dissolution liberates the drug molecule for release and subsequent diffusion controls the

release of drug out of the matrix." *Id.* at 18. Petitioner, on the other hand, contends that our construction in the related case was correct, and that the plain and ordinary meaning of the term is "dissolution of the drug in the matrix followed by diffusion of the drug out of the matrix." Pet. Reply 2.

The main difference between the parties' constructions is whether diffusion must control the rate of release of drug out of the matrix. After considering the parties' arguments, we adopt Petitioner's construction as the broadest reasonable interpretation consistent with the Specification.

To construe the term, we start with the language of the claim. Claim 1 recites a "controlled-release oral drug dosage form" that "releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid." We determine that nothing in the claim language requires that the drug release be "at a rate controlled by the rate of diffusion," as Patent Owner asserts. To the extent Patent Owner suggests that its construction is dictated by the fact that the claim recites a "controlled-release" drug formulation for a highly soluble drug, we are not persuaded. In particular, we note that Patent Owner's own declarant, Dr. Harold B. Hopfenberg, testified that those parameters do not necessarily require release by dissolution and diffusion:

> Q: Is it your opinion that, if you use a swellable polymer in a highly soluble drug and you get extended release that meets the requirements of Claim 1, that you must necessarily be releasing by dissolution and diffusion?
>
> A. Could you repeat that?
>
> (The record was read by the reporter.)
>
> THE WITNESS: No.

Ex. 1072, 44:17–24.

Patent Owner also argues that the Specification supports its narrowed construction. For example, Patent Owner asserts that the "focus of the '475 Patent is on slowing the rate of diffusion." PO Resp. 16. Patent Owner also notes that the Specification "states the invention disclosed 'is achieved by using a formulation in which the drug is incorporated in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the drug primarily by diffusion.'" *Id.* at 17 (quoting Ex. 1001, 5:57–62).

We are not persuaded. Our reviewing court has warned that, "[a]bsent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification or prosecution history when those sources *expressly disclaim* the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (emphasis added). Here, the Specification does not expressly disclaim other mechanisms of drug release that are not controlled by diffusion. Indeed, many of the '475 patent claims are directed to drug dosage forms that release the drug by erosion or diffusion, reciting that the dosage form "releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix." Ex. 1001, claim 19; *see also* independent claims 22, 24, 27, 28, 29, 30, 32, 33, 34, 37, 38, 39, 40, 42, 43, and 44 (reciting similar "erosion or diffusion" limitations). Thus, to the extent Patent Owner asserts those claims have sufficient written description support, the '475 patent Specification clearly is not limited to dosage forms where drug release is controlled by the rate of diffusion.

Finally, our reviewing court "counsels the PTO to avoid the temptation to limit broad claim terms solely on the basis of specification

passages." *Bigio*, 381 F.3d at 1325. Accordingly, while the Specification's "Summary of the Invention" may state that the drug formulation "releases the drug primarily by diffusion" (Ex. 1001, 5:56–62), we decline to import that limitation from the Specification. *See Bigio*, 381 F.3d at 1325 (affirming Board's construction that declined to limit "hair brush" to scalp hair brushes despite statements in the "Objects of the Invention").

Patent Owner alternatively argues that a person of ordinary skill in the art would have understood the plain and ordinary meaning of claim 1 to require that "dissolution liberates the drug molecule for release and subsequent diffusion controls the release of drug out of the matrix." PO Resp. 17–18. We are not persuaded. As explained above, nothing in the claim language requires that diffusion must control the release of the drug. And, contrary to Patent Owner's suggestion, the testimony by Petitioner's declarant, Dr. Roland Bodmeier, that drug "is released by diffusion" does not amount to an admission that drug release is *controlled* by the rate of diffusion. *See id.* Rather, Dr. Bodmeier's testimony is consistent with our interpretation of the plain and ordinary meaning of the claim.

Upon considering the parties' arguments and evidence, we determine that the broadest reasonable interpretation of "releases said drug . . . by the dissolution and diffusion of said drug out of said matrix" is "releases the drug by dissolution of the drug in the matrix followed by diffusion of the drug out of the matrix."

B. Principles of Law

To prevail in its challenges to the patentability of the claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

C. The Level of Ordinary Skill in the Art

In large part, the parties agree as to the level of ordinary skill in the art. Pet. 7; PO Resp. 10. Both agree that a person of ordinary skill in the art would be a person with a Ph.D. degree in at least pharmaceutical science, chemistry, or chemical engineering along with at least two years of industry experience in the development of controlled-release oral dosage forms.

Pet. 7; PO Resp. 10. Both also agree that a person of ordinary skill in the art may have an equivalent level of skill through similar education, training, and industry experience. Pet. 7; PO Resp. 10. In light of the parties' agreement, we adopt that description of the level of ordinary skill in the art for purposes of this proceeding.

D. Obviousness over Baveja, the '837 Patent, and the '548 Patent

Petitioner asserts that claims 1, 8, 9, 13–15, and 61 of the '475 patent are unpatentable as obvious over Baveja, the '837 patent, and the '548 patent. Pet. 27–33; Pet. Reply 3–10. Petitioner relies on the Declaration of Dr. Bodmeier. Ex. 1004 ¶¶ 115–31. Patent Owner disagrees with Petitioner's assertions (PO Resp. 28–39), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 155–68).

1. Baveja (Ex. 1005)

Baveja discloses a dosage form comprised of a swellable hydrophilic matrix that exhibits zero-order (i.e., constant) release of a drug. Ex. 1005, Summary. Baveja uses β-adrenergic blockers propranolol hydrochloride, alprenolol hydrochloride, and metoprolol tartrate as model drugs. *Id.* at 40. Baveja describes tablets with different ratios of HPMC, sodium carboxymethylcellulose ("Na CMC"), and drug, which are then subjected to an in vitro dissolution study. The in vitro dissolution study involves placing the tablets into a dissolution rate test apparatus with diluted HCl (pH 3.0) for three hours and then in 0.2 M phosphate buffer (pH 7.4) for another 9 hours. *Id.*

The results of the dissolution studies for tablets formed from just HPMC and drug are shown in Figures 1–3. For example, Figure 2 is reproduced below:

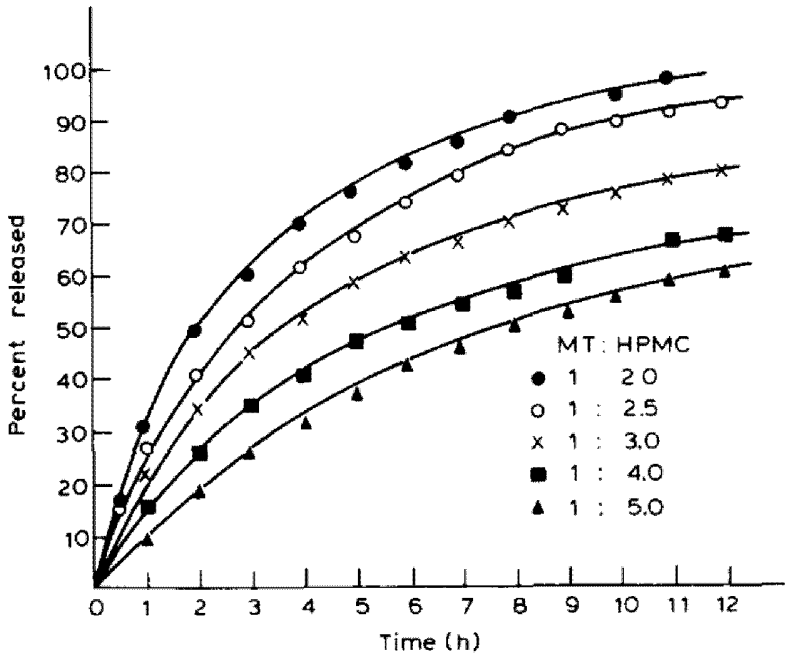

Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

Figure 2 illustrates the cumulative percent of metoprolol tartrate released as a function of time from tablets containing metoprolol tartrate and HPMC in the ratios shown. *Id.* at 41.

As explained by Baveja, the rate of release of the tablets made of drug and HPMC decreases with time, which may be due to "an increase in diffusional path length for the drug[,] which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer." *Id.*

Baveja also describes tablets formed from HPMC, Na CMC, and drug in varying amounts that exhibit a nearly zero-order rate of release. *Id.*, Abstract.

2. The '837 Patent (Ex. 1010)

The '837 patent relates to the field of alkyl-substituted cellulose-based sustained-release drug dosage forms.[8] Ex. 1010, 1:17–19. Specifically, the dosage form disclosed in the '837 patent comprises a plurality of solid particles of a drug dispersed within a non-crosslinked alkyl-substituted cellulose that "swells unrestricted dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote gastric retention of the pellets in fed-mode induced patients." *Id.* at 1:58–65. The '837 patent teaches that the particles will normally swell to a size of about 6 to 18 mm. *Id.* at 5:8–12. According to the '837 patent specification, the dosage form is particularly useful for delivering drugs in a sustained manner within the stomach. *Id.* at 2:39–43.

The '837 patent also discloses drug release experiments using drug dosage forms comprised of hydroxypropylcellulose ("HPC") and aspirin ("ASA"). *Id.* at 7:25–57. The results of the drug release experiments, which were performed in simulated gastric fluid, are shown in Figure 1, which is reproduced below.

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[8] Patent Owner asserts the '837 patent "is not prior art under 35 U.S.C. § 102(b)." PO Resp. 24. Unlike with the '280 patent in IPR2014-00377, Patent Owner does not dispute that the '837 patent is applicable prior art to the '475 patent under 35 U.S.C. § 102(e), as the Petition asserts. *See* Pet. 29.

Fig. 1

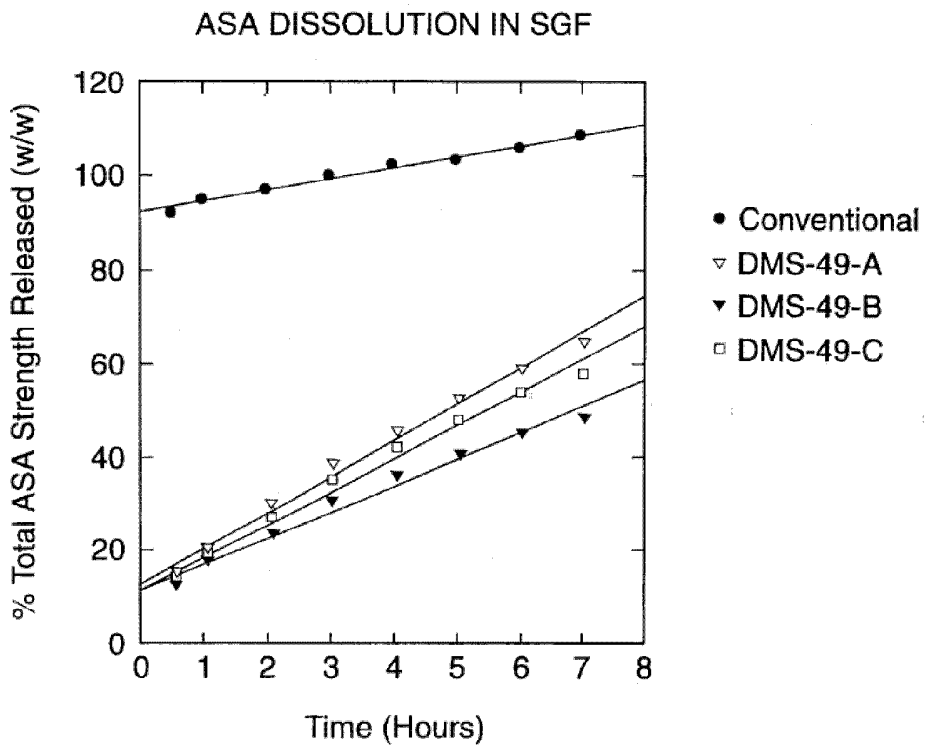

Figure 1 depicts the percentage of aspirin released over time for the various drug formulations tested, including conventional aspirin without HPC. *Id.* at 7:47–52. The release of aspirin was measured at various intervals up to seven hours. *Id.*

3. The '548 Patent (Ex. 1011)

The '548 patent issued on October 3, 1989, and relates to a controlled-release dosage form comprising a drug and at least two different cellulose ethers. Ex. 1011, 1:12–16. According to the '548 patent specification, "[an] object of the present invention is to provide a dosage form of delivering a drug in the gastrointestinal tract that substantially avoids a premature disintegration." *Id.* at 3:1–4. The '548 patent specification also states that the disclosed invention "delivers a drug at a rate of dosage form release that

corresponds to the rate of change of the integrity of the dosage form over a prolonged period of at least eight hours." *Id.* at 3:4–7.

Moreover, the dosage form uses cellulose ethers, which swell extensively when hydrated and lessens direct drug contact with mucosal tissues. *Id.* at 11:23–26. The drug delivery matrix is suitable for gastric retention over the releasing lifetime of the dosage system. *Id.* at 10:65–68. Furthermore, "when all the drug is released, the system bioerodes into innocuous particles and dissolved polymers that pass from the gastrointestinal tract." *Id.* at 10:68–11:3.

4. Analysis

Petitioner asserts that claims 1, 8, 9, 13–15, and 61 of the '475 patent are unpatentable as obvious over Baveja, the '837 patent, and the '548 patent. We have reviewed the arguments and evidence presented by both parties, and we are not persuaded that Petitioner has shown by a preponderance of the evidence that the claims would have been obvious over the cited references.

Petitioner argues that "[t]he only difference between the disclosure in Baveja and claim 1, is that Baveja does not expressly disclose certain inherent properties and release characteristics of its formulations." Pet. 28. Specifically, Petitioner asserts that two limitations of claim 1 are disclosed inherently, not expressly, in Baveja: (1) "polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode" (i.e., the "swelling" limitation) (Pet. 35–36); and (2) "remains substantially intact until all of said drug is released" (i.e., the "substantially intact" limitation) (*id.* at 36).

Looking first at the limitations that Petitioner contends are expressly disclosed, Patent Owner disagrees with Petitioner's contentions, arguing that Baveja does not disclose, either expressly or inherently, drug release by "dissolution and diffusion." PO Resp. 29–30. Indeed, Patent Owner contends that Baveja actually teaches away from drug release by dissolution and diffusion because it describes the dosage form relied upon by Petitioner as having a "major disadvantage" because it does not exhibit zero-order release. *Id.* (citing Ex. 1005, 40). We find, however, that Baveja teaches "dissolution and diffusion" expressly when it states that "Figs. 1–3 reveal that the rate of release decreased with time and this may be due to an increase in diffusional path length for the drug which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer." Ex. 1005, 41. Moreover, the fact that Baveja may prefer dosage forms that exhibit zero-order release, over those that do not, does not teach away from the claimed invention. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("This court has further explained that just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

For the remaining limitations of claim 1 that Petitioner contends are expressly disclosed, based on the evidence presented, we are persuaded that Petitioner has established that Baveja teaches those limitations expressly. Pet. 12–16; Ex. 1004 ¶¶ 70–71, 77–79. We further agree with Petitioner that Baveja does not expressly disclose the "swelling" limitation and the "substantially intact" limitation. *See* Pet. 12–13, 15–16.

Petitioner, however, asserts that Baveja inherently teaches the "swelling" and "substantially intact" limitations. Pet. 35–36. To prove

inherency, Petitioner must establish that "the missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). We are not persuaded that Petitioner has met this test for either limitation.

Regarding the "swelling" limitation, Petitioner asserts that Baveja discloses a tablet that is 11 mm in diameter prior to imbibition of water and contains 25% alprenolol HCl and 75% HPMC. Pet. 12–13; *see* Ex. 1005, Fig. 1. Petitioner concludes that Baveja inherently discloses a dosage form that swells to a size sufficient to promote retention in the stomach during the fed mode. Pet. 35 (citing Ex. 1004 ¶¶ 72–76). Petitioner bases its argument in part on the '475 patent Specification's disclosure that "[p]articles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours." Ex. 1001, 11:67–12:2. Although Baveja does disclose a "swelling front" (Ex. 1005, 41), we are not persuaded that Petitioner has established that Baveja inherently teaches the entirety of the "swelling" limitation. Specifically, we are not persuaded that Petitioner has shown that Baveja necessarily teaches swelling that "will promote retention in the stomach during the fed mode." For example, it is not clear whether having a tablet that is 11 mm in size in diameter (without knowing any other dimension of the tablet) will necessarily remain in the stomach.

As for the "substantially intact" limitation, Petitioner argues that Baveja's formulation inherently would remain substantially intact. Pet. 36. As support, Petitioner relies on both the testimony of Dr. Bodmeier and the test results of Dr. Kinam Park. *Id.* According to Petitioner, Dr. Park re-created two formulations in Baveja to determine the release kinetics and swelling properties of the dosage forms. Pet. 19. As explained in our

Decision to Institute, however, because Dr. Park did not provide evidence of a positive control, we cannot conclude with sufficient certainty that Dr. Park's dosage forms were, in fact, the same dosage forms disclosed by Baveja. Dec. Inst. 11. During oral argument, Petitioner accepted our finding. Tr. 29:21–22 ("We accept the Board's conclusion regarding the prior test results . . . ."). And, as explained in our Decision to Institute, we do not give persuasive weight to Dr. Bodmeier's unsupported opinion that the Baveja tablets will remain substantially intact. Dec. Inst. 11–12. Accordingly, we are not persuaded that Baveja inherently teaches the "substantially intact" limitation.

Petitioner provides, however, alternative sources for teaching these two limitations missing from Baveja. First, Petitioner asserts that the '837 patent discloses expressly the "swelling" and "substantially intact" limitations. Pet. 37–38. We agree. The '837 patent discloses that the dosage form "swells unrestricted dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote gastric retention of the pellets in fed-mode induced patients." Ex. 1010, 1:62–66. The '837 patent also discloses that the drugs are dispersed in the "selected alkyl-substituted cellulose such as hydroxyethylcellulose or hydroxy propylcellulose," and that "because these polymers dissolve very slowly in gastric fluid, the particles maintain their integrity over at least a substantial portion (i.e., at least about 90% and preferably over 100% of the intended dosing period)." *Id.* at 4:31–46.

Second, Petitioner asserts that the '548 patent teaches the "swelling" and "substantially intact" limitations. Pet. 41–42. We are not persuaded, however, that the cited portions of the '548 patent teach or suggest either of

these limitations. For example, as Patent Owner notes (PO Resp. 34), Petitioner points to nothing in the '548 patent that suggests the dosage form swells to a size exceeding the pyloric diameter "in fed mode," as required by the "swelling" limitation. Nor are we persuaded that the '548 patent's teaching that the dosage form "exhibit[s] better mechanical integrity" teaches or suggests a dosage form that remains "substantially intact," as defined by the Specification, particularly in light of the '548 patent's disclosure of drug release by erosion. *See id.* at 36; *see also* Ex. 1017, 3:1–7 (describing drug release at a rate that "corresponds to the rate of change of the integrity of the dosage form over a prolonged period of at least eight hours").

Notwithstanding our findings with respect to the '548 patent, we are persuaded that Petitioner has established that each limitation of claim 1 was known in the art, as evidenced by the teachings of Baveja and the '837 patent. A patent, however, "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Petitioner must also show that there was a reason to combine those elements to achieve the claimed invention with a reasonable expectation of success. *See PAR Pharm.*, 773 F.3d at 1193. To make that determination, we can look to "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art." *Id.* We can also look to the nature of the problem to be solved. *In re Gartside*, 203 F.3d 1305, 1319 (Fed. Cir. 2000) (holding that suggestion to combine "may come from, *inter alia*, the teachings of the references themselves and, in some cases, from the nature of the problem to

be solved"). After considering the parties' arguments and evidence, however, we are not persuaded that Petitioner has made a sufficient showing that a person of ordinary skill would have combined the teachings in the manner contended by Petitioner.

Petitioner argues that a person of ordinary skill in the art would have been led to combine the teachings of Baveja and the '837 patent for several reasons.[9] Pet. 38. First, Petitioner argues that the references have interrelated teachings. According to Petitioner, both references are directed to controlled-release dosage forms that contain HPMC with similar drug-to-polymer weight ratios. *Id.*; Ex. 1016 ¶ 121. For example, claim 1 of the '837 patent recites a drug to polymer ratio of about 1:9 to 9:1. Ex. 1010, claim 1. Baveja's matrix contains a drug-to-polymer ratio that falls within the weight ratio range claimed by the '837 patent. Pet. 38 (citing Ex. 1005, Figs. 1 and 2); Ex. 1004 ¶ 121. Moreover, Petitioner argues that both references teach drug formulations for high solubility drugs. Pet. 38–39; Ex. 1004 ¶ 122. Petitioner and its declarant, Dr. Bodmeier, assert also that "the advantages of formulations retained in the stomach and techniques for creating swellable polymer formulations retained in the stomach, were well known by a [person of ordinary skill in the art]." Pet. 36; Ex. 1004 ¶ 117. Petitioner then concludes that "it would be natural for a POSA to combine

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[9] Petitioner argues also that a person of ordinary skill in the art would have been motivated to combine Baveja and the '548 patent to achieve the claimed invention. Pet. 41–42. Because we are not persuaded that the '548 patent teaches the "swelling" and "substantially intact" limitations, we do not address further the proposed combination of Baveja and the '548 patent.

the teachings of these two references to arrive at the formulation in claim 1 of the '280 patent." Pet. 39; Ex. 1004 ¶ 122.

Second, Petitioner argues that a person of ordinary skill in the art would have had a reason to combine Baveja and the '837 patent given the nature of the problem to be solved: "to formulate a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." Pet. 41. As such, Petitioner argues that a person of ordinary skill in the art reading Baveja would look to the '837 patent "to confirm that the same polymer will in fact be retained in the stomach and remain substantially intact." *Id.*

In response, Patent Owner argues that Petitioner has failed to demonstrate a motivation to combine the cited references with a reasonable expectation of success. Patent Owner challenges Dr. Bodmeier's statement that it would be "natural" to combine Baveja and the '837 patent. PO Resp. 37. According to Patent Owner, Dr. Bodmeier fails to provide any substantive evidence to support his testimony that it would take him "a week" to come up with the claimed invention. *Id.* at 38 (quoting Ex. 2018, 80:19–81:8). In contrast to Dr. Bodmeier's testimony, Patent Owner notes that Jenny-Louie Helm, an inventor of the '475 patent ("Inventor Helm"), testified that it "took years of research and testing in the laboratory to manipulate different variables, such as type of polymer, molecular weight, particle size, dosage size, matrix chemical structure, and manufacturing processes, to come up with the claimed inventions." *Id.*; Ex. 2016 ¶ 21 (Helm Decl.) ("It took me three years testing various polymers with guidance of Dr. Shell to achieve the Captopril formulation that contained the

aspects of the claims of the '475 and '280 Patents."). Consistent with Inventor Helm's testimony, Patent Owner asserts that its declarant, Dr. Hopfenberg, testified that a person of ordinary skill in the art would not have reasonably expected to successfully achieve the claimed invention given that a "vast array of structural considerations affect polymer and matrix properties." *Id.* at 38–39 (citing Ex. 2010 ¶¶ 59, 153, 166–67).

On the record developed at trial, we are not persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reason to combine the references with a reasonable expectation of success. Although the references may have interrelated teachings, as Petitioner asserts, Petitioner has not explained persuasively *how or why* a person of ordinary skill in the art would have combined the "swelling" and "substantially intact" features of the '837 patent with the dosage formulation of Baveja.

In its Reply, Petitioner asserted another reason to combine the cited references:

> A [person of ordinary skill in the art] would look to (1) Baveja to learn how to adjust the rate of high solubility drug release by varying the drug-to-polymer (HPMC) weight ratio and (2) either the '837 or the '548 patent to confirm that the same type of polymer used in Baveja will (a) swell to a size large enough to promote retention in the stomach during the fed mode, and (b) remain substantially intact until all of the drug is released.

Pet. Reply 8–9; Ex. 1004 ¶¶ 125–30. But here, again, Petitioner speaks in generalizations and does not explain persuasively *why* a person of ordinary skill in the art, learning from Baveja how to adjust the rate of drug release by varying the drug-to-polymer weight ratio, would need or want to look to the '837 patent to "confirm" the "swelling" and "substantially intact" properties.

See InTouch Techs., Inc. v. VGO Commc'ns, Inc., 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing district court's judgment of invalidity where expert's testimony "was vague and did not articulate reasons why a person of ordinary skill in the art at the time of the invention would combine these references").

To the extent Petitioner relies on the nature of the problem to be solved to supply the reason for the combination, we remain unpersuaded. Petitioner's recitation of the nature of the problem to be solved is essentially a recitation of claim 1 itself: "to formulate a swellable, controlled release oral dosage form for releasing a high solubility drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." Pet. 41. As our reviewing court has recently reminded us, however, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)). As such, the Federal Circuit stated that when considering the reason to combine, "the problem examined is not the specific problem solved by the invention." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Here, the claim represents the specific problem solved by the invention, rather than the general problem facing the inventors. Thus, we find that by defining the nature of the problem to be solved as the specific problem solved by the invention, Petitioner has relied on impermissible hindsight to supply the reason to combine Baveja and the '837 patent. *See id.* (affirming the district court's recognition that "an overly narrow 'statement of the problem [can] represent[] a form of prohibited

reliance on hindsight, [because] [o]ften the inventive contribution lies in defining the problem in a new revelatory way'") (quoting *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (alterations in original)).

Even if we were to find that Petitioner has established that a person of ordinary skill in the art would have had a reason to combine the teachings of Baveja and the '837 patent, we are still not persuaded that Petitioner has established that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

Petitioner argues that at the time of the invention, a person of ordinary skill in the art "understood how to achieve" the claimed drug formulation. Pet. 37. For example, Petitioner and its declarant argue that a person of ordinary skill in the art would have known "techniques for creating swellable polymer formulations retained in the stomach." Pet. 36 (citing Ex. 1004 ¶ 117). Petitioner also argues that a person of ordinary skill in the art would have known how to construct a matrix that would remain intact because it was well known that "increasing the viscosity of HPMC (based on grade) or the concentration (by altering the drug-to-polymer weight ratio) strengthens the matrix, resulting in a dosage form that would remain physically intact over the dosing period." Pet. 36–37 (citing Ex. 1004 ¶ 119).

We are not persuaded that a person of ordinary skill in the art would have had a reasonable expectation of success, in part, because both parties' declarants testified about the number of formulation considerations at play when preparing a drug formulation. For example, Petitioner's declarant testified that there were formulation considerations such as "molecular weight, chemical substitution, particle size, hydration rate effect, polymer

content, dosage form, dosage size and manufacturing processes." Ex. 1004 ¶ 37. Similarly, Patent Owner's declarant stated that "[a] person of ordinary skill in the art understands that formulation of a polymer matrix involves a vast array of interacting 'formulation considerations' affecting polymer and matrix properties." Ex. 2010 ¶ 152; *id.* ¶¶ 59, 153, 166–67. Despite this testimony from its own declarant (as confirmed by Patent Owner's declarant), we find that Petitioner does not address sufficiently why a person of ordinary skill in the art would believe it could modify the formulation of Baveja to incorporate the "swelling" and "substantially intact" features of the '837 patent without, for example, affecting the other properties of the original Baveja formulation (e.g., the drug release profile). Nor has Petitioner identified any combinations of Baveja and the '837 patent that would be most promising to try. As such, we reach the same conclusion as the Federal Circuit in *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013). That is, we find that "[w]ithout a reasonable expectation of success or clues pointing to the most promising combinations, an artisan could have spent years experimenting without success." *Id.*

Finally, in its Reply, Petitioner argues that "[e]ven if the Board accepts that Dr. Park's tablets are not identical to Baveja's tablets, Baveja's disclosures led Dr. Park to create dosage forms that fall within the scope of claim 1 using techniques well-known to a POSA, . . . confirming that the claims are obvious over Baveja." Pet. Reply 5.

The problem with Dr. Park's test results is that he did not testify from the perspective of a person of ordinary skill in the art *at the time of the invention*. Specifically, Dr. Park attested that "[i]n performing the testing set forth in this Declaration, [he] considered and relied upon [his] education,

background, and years of experience in the field of pharmaceutical sciences." Ex. 1014 ¶ 13. Thus, even if we did accept Dr. Park's testimony as true, it is irrelevant to our obviousness analysis. *InTouch Techs.*, 751 F.3d at 1352 (stating expert's testimony as to what a skilled artisan could accomplish at the time the testimony was given "is not the relevant inquiry" to what a skilled artisan would have understood as of the time of the invention).

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 8, 9, 13–15, and 61 are unpatentable as obvious over Baveja, the '837 patent, and the '548 patent.

E. Obviousness of Claim 10 over Baveja, Kim, the '837 Patent, and the '548 Patent

Petitioner asserts that claim 10 of the '475 patent is unpatentable as obvious over Baveja, Kim, the '837 patent, and the '548 patent, relying on the Declaration of Dr. Bodmeier. Pet. 45–48; Pet. Reply 10; Ex. 1004 ¶¶ 153–58. Patent Owner disagrees with Petitioner's assertions (PO Resp. 39–41), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 169–75).

1. Kim (Ex. 1012)

Kim discusses drug release from compressed tablets manufactured with a powder mixture of poly(ethylene oxide) ("PEO"), a drug, and magnesium stearate. Ex. 1012, 303. In one example, Kim describes a dosage form wherein the PEO has an average molecular weight of 4,000,000. *Id.*

2. Analysis

Claim 10 of the '475 patent depends from claim 1 and further requires a polymeric matrix formed of PEO at a molecular weight of at least about 4,000,000. Ex. 1001, claim 10. As determined above, we find that the combination of Baveja and the '837 patent teaches each limitation of claim 1. We also find that Kim teaches the additional limitation of claim 10, which Patent Owner does not dispute. *See* PO Resp. 39–41.

Because claim 10 depends from claim 1, we determine, for the same reasons stated above, that Petitioner has failed to establish that a person of ordinary skill in the art would have had a reason to combine the teachings of Baveja, Kim, the '837 patent, and the '548 patent to achieve the claimed invention with a reasonable expectation of success.

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claim 10 is unpatentable as obvious over Baveja, Kim, the '837 patent, and the '548 patent.

F. Obviousness over Colombo, the '837 Patent, and the '548 Patent

Petitioner asserts that claims 1, 8, 9, 13, 14, 61, and 62 of the '475 patent are unpatentable as obvious over Colombo, the '837 patent, and the '548 patent, relying on the Declaration of Dr. Bodmeier. Pet. 50–56; Pet. Reply 10–13; Ex. 1004 ¶¶ 132–52, 163–68. Patent Owner disagrees with Petitioner's assertions (PO Resp. 41–45), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 176–80).

1. Colombo (Ex. 1006)

Colombo relates to swellable matrix systems in the form of a tablet comprising a mixture of the drug diltiazem, HPMC, ethylcellulose, and

mannitol. Ex. 1006, 44. Colombo discloses three different matrices: Case 0, the plain matrix; Case 1, the matrix coated with cellulose acetate propionate ("CAP") on one face; and Case 2, the matrix coated with CAP on both faces. *Id.* Colombo describes "[s]welling and release experiments" in which the matrices were swollen in deionized water for 120 minutes, and the drug release measurements were obtained concomitantly with the matrix swelling observations. *Id.*

Colombo describes and depicts the morphological changes in the matrices over time, observing that, in the uncoated system (Case 0), "[v]ery quickly (after 15 min) the swelling of the matrix moves both in axial and radial directions." *Id.* Colombo also discloses the drug release profiles of the systems. *Id.* at 45. Figure 5 of Colombo is reproduced below:

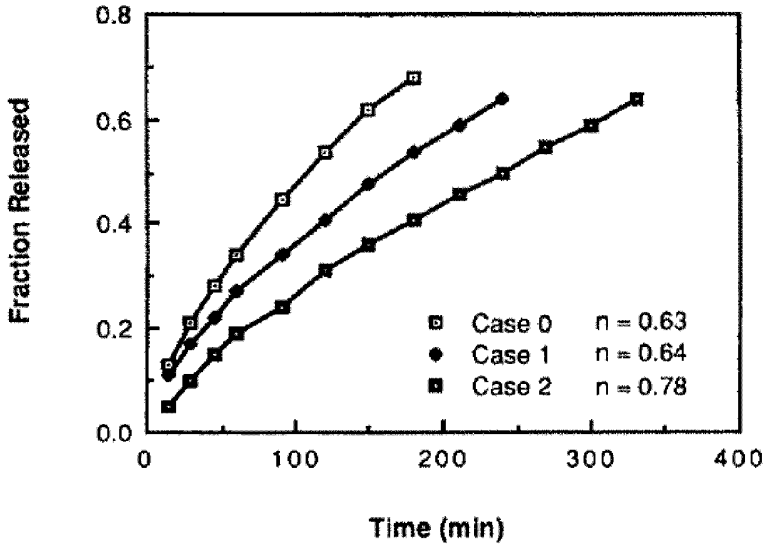

Fig. 5. Drug release profiles of the systems. Calculated values of exponent *n* of Eqn 2 are also shown.

Figure 5 depicts the fraction of diltiazem released over time for the Case 0, Case 1, and Case 2 matrices.

2. Analysis

Petitioner argues that Colombo anticipates each limitation of claim 1. Pet. 50. As explained in our Decision to Institute, we are not persuaded that Colombo anticipates at least because Colombo does not teach certain properties "upon immersion in gastric fluid," as required by claim 1. Dec. Inst. 13–15. Alternatively, Petitioner asserts that claims 1, 8, 9, 13, 14, 61, and 62 of the '475 patent are unpatentable as obvious over Colombo, the '837 patent, and the '548 patent. Pet. 50–56. Petitioner appears to assert that, to the extent Colombo does not teach the "swelling" and "substantially intact" limitations, those limitations are taught by the '837 patent. As above, we find that the '837 patent teaches those limitations (and the '548 patent does not).

Petitioner further contends that a person of ordinary skill in the art would have been motivated to combine the teachings of Colombo and the '837 patent given the nature of the problem to be solved (identified above) and the interrelated teachings of the art. *Id.* at 52–53. In particular, Petitioner contends that the drug to polymer weight ratios are similar, and that both disclose formulations containing the drug diltiazem. *Id.*

For similar reasons stated above with respect to Baveja and the '837 patent, we find that Petitioner has not established that a person of ordinary skill in the art would have had a reason to combine the references to achieve the claimed invention with a reasonable expectation of success. Once again, Petitioner frames the nature of the problem to be solved too narrowly, indicating a hindsight bias. *See Insite Vision*, 783 F.3d at 859. Moreover, as Patent Owner argues, Petitioner "offered no credible basis for showing that one of skill in the art would have reason or motivation to combine the prior

art references to make the claimed invention." PO Resp. 45. We find that Petitioner does not explain persuasively why a person of ordinary skill in the art would have had a reasonable expectation of success beyond just the knowledge that each limitation of the claim was known in the art at the time of the invention.

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 8, 9, 13, 14, 61, and 62 of the '475 patent are unpatentable as obvious over Colombo, the '837 patent, and the '548 patent.

G. Secondary Considerations of Nonobviousness

In light of our determination that Petitioner has not shown by a preponderance of the evidence that any of the challenged claims are unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

III. MOTIONS TO EXCLUDE EVIDENCE

Both parties filed motions to exclude evidence offered by the other side. The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence ("FRE"). *See* 37 C.F.R. §§ 42.20(c), 42.62(a). We address each party's motion in turn.

1. Petitioner's Motion to Exclude Evidence

Petitioner moves to exclude portions of Dr. Hopfenberg's declaration and a claim chart for Gralise® (Ex. 2013) as improperly incorporated by reference and as irrelevant because they are improperly incorporated. Paper 42, 3–5. We decline to do so. As explained in our prior Order (Paper 31), to the extent any such violations have occurred, we have not considered

such evidence in reaching our decision. Therefore, we dismiss Petitioner's motion as moot.

Petitioner also moves to exclude certain testimony of Inventor Helm. Paper 42, 10–13. We decline to do so. To the extent we have relied on the testimony of Inventor Helm, that testimony was based on her own work. *See* Ex. 2016 ¶ 21 (testifying how long it took her to develop an embodiment of the claims). Such testimony based on her own personal knowledge is relevant and proper lay witness testimony under FRE 701, 602, and 401/402/403. Accordingly, we deny Petitioner's motion as to this evidence.

Petitioner also moves to exclude certain evidence relating to Patent Owner's assertions of commercial success, licensing, long-felt but unmet need, and unexpected results. Paper 42, 5–15. Given our determination that we need not reach Patent Owner's evidence of secondary considerations, we need not reach the merits of Petitioner's Motion to Exclude.

2. Patent Owner's Motion to Exclude Evidence

Patent Owner also moves to exclude (1) Exhibits 1058, 1059, and 1065 (Paper 49, 3–8); (2) Exhibit 1071 and the related testimony of Dr. Bodmeier (*id.* at 8–10); and (3) portions of the cross-examination testimony of Dr. Eric Gaier (*id.* at 11–13). Because we did not rely on any of these exhibits or testimony in reaching our Decision here, we dismiss Patent Owner's motion to exclude this evidence as moot.

IV. CONCLUSION

We conclude that Petitioner has not shown by a preponderance of the evidence that claims 1, 8–10, 13–15, 61, and 62 of the '475 patent are unpatentable under 35 US.C. § 103.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 8–10, 13–15, 61, and 62 of the '475 patent are not held unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is *denied in part and otherwise dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *denied in part and otherwise dismissed*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2014-00378
Patent 6,340,475 B2

PETITIONER:

Gasper J. LaRosa
gjlarosa@jonesday.com

Kelsey I. Nix
knix@jonesday.com

Lynda Q. Nguyen
lqnguyen@jonesday.com

PATENT OWNER:

Judy M. Mohr
JMohr@MWE.com

Paul Andre
PAndre@kramerlevin.com

Geoffrey G. Hu
GHu@kramerlevin.com

Trials@uspto.gov
571-272-7822

Paper 72
Entered: July 8, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PURDUE PHARMA L.P.,
Petitioner,

v.

DEPOMED, INC.,
Patent Owner.

Case IPR2014-00379
Patent 6,340,475 B2

Before ERICA A. FRANKLIN, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Purdue Pharma L.P. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 43, 54, 55, 57, 58, and 66 of U.S. Patent No. 6,340,475 B2 (Ex. 1001, "the '475 patent"). Paper 1 ("Pet."). Depomed, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). On July 10, 2014, we instituted an *inter partes* review of claims 43, 54, 55, 57, 58, and 66 on certain grounds of unpatentability alleged in the Petition. Paper 9 ("Dec. Inst."), 22. Patent Owner timely filed a Response (Paper 23, "PO Resp."), to which Petitioner timely filed a Reply (Paper 34, "Pet. Reply").

Both parties filed motions to exclude certain exhibits and testimony. Paper 40 (Petitioner); Paper 47 (Patent Owner). Both parties opposed the other's motion to exclude. Paper 55 (Patent Owner Opposition); Paper 50 (Petitioner Opposition). And both parties filed reply briefs in support of their motions to exclude. Paper 57 (Petitioner Reply); Paper 58 (Patent Owner Reply).

Patent Owner also filed a Motion for Observation (Paper 45) on certain cross-examination testimony of Petitioner's declarant Dr. Eric M. Gaier, and Petitioner filed a Response (Paper 51).

A consolidated oral hearing for this proceeding and Cases IPR2014-00377 and IPR2014-00378 was held on March 19, 2015, a transcript of which has been entered in the record.[1] Paper 71 ("Tr.")

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[1] Petitioner and Patent Owner filed Objections to Demonstrative Exhibits. Paper 66 (Patent Owner); Paper 67 (Petitioner). In this Final Written Decision, we rely directly on the arguments presented properly in the

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 43, 54, 55, 57, 58, and 66 of the '475 patent are unpatentable.[2]

A. Related Proceedings

Petitioner and Patent Owner identify various district court actions involving the '475 patent, including an action involving the parties titled *Depomed, Inc. v. Purdue Pharma L.P.*, No. 3:13-00571 (D.N.J.). Pet. vii; Paper 5, 2–3.

Petitioner has also filed two related petitions for *inter partes* review. One petition involves U.S. Patent No. 6,635,280 B2, which is a continuation of the '475 patent. *See* IPR2014-00377. The other petition involves the '475 patent, as well, but challenges different claims. *See* IPR2014-00378. We issue Final Written Decisions in those two related proceedings concurrently herewith.

B. The '475 Patent (Ex. 1001)

The '475 patent relates to drugs formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic

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parties' briefs and the evidence of record. The demonstrative exhibits were only considered to the extent they are consistent with those arguments and evidence.

[2] On February 20, 2015, Patent Owner objected to Petitioner's use of a condensed font in Petitioner's Reply paper. Petitioner, however, appears to have used the same condensed font throughout this proceeding. *Compare* Pet. *with* Pet. Reply (using same font). In light of Patent Owner's late objection, we deem the objection to be waived.

polymers that swell upon imbibition of water to a size large enough to promote gastric retention of the drug during the fed mode. Ex. 1001, Abstract. Drugs administered by conventional tablets generally become available to body fluids at a high rate initially, followed by a rapid decline. *Id.* at 1:31–33. To address that issue, controlled drug delivery systems were introduced in the 1970's. *Id.* at 1:35–37. Many of the controlled delivery systems utilize hydrophilic, polymeric matrices that provide controlled release of sparingly soluble drugs. For soluble drugs, however, such matrices do not provide adequate control of drug release. *Id.* at 1:45–50.

The claimed invention allows drugs that are highly soluble in water to be administered orally in a way that will prolong their release rate throughout the duration of the fed mode. *Id.* at 5:32–36. This prolonged release rate reduces the problem of transient overdosing, and controls the dosage to safer and more effective levels over an extended period of time. *Id.* at 5:36–41. Moreover, particles exceeding about 1 cm in size are larger than the pylorus and are retained in the stomach for approximately 4 to 6 hours. *Id.* at 11:66–12:2. The Specification states that these benefits are due, in part, to using a polymeric matrix that is water-swellable rather than just hydrophilic, that has an erosion rate substantially slower than its swelling rate, and that releases the drug primarily by diffusion rather than erosion. *Id.* at 5:57–62. Preferred polymeric matrices include water-swellable polymers such as hydroxypropylmethylcellulose ("HPMC") and poly(ethylene) oxide ("PEO"). *Id.* at 7:54–8:51.

C. Illustrative Claim

Claim 43 is illustrative and is reproduced below:

> 43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:
>
> (a) swells upon imbibition of gastric fluid is to a size large enough to promote retention in the stomach during said fed mode,
>
> (b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,
>
> (c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,
>
> (d) releases substantially all of said drug within about ten hours after such immersion, and
>
> (e) remains substantially intact until all of said drug is released,
>
> thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

Claims	**Basis**	**References**
43, 54, 55, 57, 58, and 66	§ 102	the '803 patent[3]

[3] Wong et al., US 6,120,803, issued Sept. 19, 2000 (Ex. 1005)

Claims	Basis	References
43, 57, 58, and 66	§ 103	the '837 patent,[4] Baveja,[5] and Colombo,[6]
54 and 55	§ 103	the '837 patent, Baveja, Colombo, and the '125 patent[7]

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279–81 (Fed. Cir. 2015). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

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[4] John W. Shell, US 5,582,837, issued Dec. 10, 1996 (Ex. 1006).
[5] Baveja et al., *Zero-Order Release Hydrophilic Matrix Tablets of β-adrenergic Blockers*, 39 INT'L J. OF PHARM. 39-45 (1987) (Ex. 1013).
[6] Colombo et al., *Drug Release Modulation by Physical Restrictions of Matrix Swelling*, 63 INT'L J. OF PHARM. 43-48 (1990) (Ex. 1014).
[7] Cherng-ju Kim, US 5,945,125, issued Aug. 31, 1999 (Ex. 1015).

1. Prior Construed Claim Terms

We construed the following claim terms in the Decision to Institute.

Claim Term	Claim	Construction
"gastric fluid"	43	"[b]oth the fluid in the stomach and simulated or artificial fluids recognized by those skilled in the art as a suitable model for the fluid of the human stomach" (Dec. Inst. 6)
"releases substantially all of said drug within about ten hours after such immersion"	43	"[a]t least 80% of the drug has been released after ten hours of immersion in gastric fluid" (Dec. Inst. 6)
"substantially intact"	43	"a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles" (Dec. Inst. 7)

Because nothing in the full record developed during trial persuades us to deviate from our prior constructions, we adopt those constructions for purposes of this Decision.

Patent Owner requests construction of two additional terms, which we address below.

2. "until all of said drug is released"

Claim 43 recites the phrase "remains substantially intact until all of said drug is released." We have construed the term "substantially intact," but Patent Owner also requests construction of the phrase "until all of said drug is released." Patent Owner asserts that the phrase should be construed

to mean "until the plateau of the dissolution profile characterizing drug release from the swollen dosage form is reached." PO Resp. 14. Petitioner does not challenge Patent Owner's construction in its Reply.

Patent Owner argues that the '475 Specification discloses drug release profiles that "show a release plateau for metformin from the dosage forms of the invention that typically does not reach 100%." *Id.* at 14–15(citing Ex. 1001, Fig. 1). Patent Owner also relies on the FDA guidance documents that state a dissolution assay should be run until "either 80% of the drug from the drug product is released or an asymptote is reached." *Id.* at 15 (quoting Ex. 2009, 6) (emphasis omitted). Finally, Patent Owner asserts that its declarant, Dr. Harold B. Hopfenberg agrees with its construction. *Id.* (citing Ex. 2010 ¶ 60).

We are not persuaded by Patent Owner's arguments. The plain meaning of "until *all* of said drug is released" is evident. If we were to adopt Patent Owner's argument that "all" can mean "less than all," we would be ignoring the plain meaning of the term. Moreover, although Patent Owner is correct that certain other embodiments in the Specification plateau at less than 100% of drug release, we note that certain embodiments do plateau at 100%. *See* Ex. 1001, Fig. 1 (curve marked by filled diamonds); *see also August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1285 (Fed. Cir. 2011) ("The mere fact that there is an alternative embodiment disclosed in the [asserted patent] that is not encompassed by [our] claim construction does not outweigh the language of the claim, especially when [our] construction is supported by the intrinsic evidence.") (citation omitted).

Furthermore, as noted above, we have determined that, as properly construed, the phrase "releases substantially all" in claim 43 means "at least

80% of the drug has been released." If we were to interpret "all" to mean the point at which the drug release profile plateaus—even if less than 80%—then it would be possible for a dosage form to release "all" of a drug, but not "substantially all" of the drug. Such an inconsistency within the claim would not be a reasonable construction of the term "all." Accordingly, we decline to construe "until all of said drug is released" as broadly as Patent Owner requests and, instead, construe it according to its plain, ordinary meaning.

3. "substantially all"

Patent Owner asserts that the term "substantially all," as it appears in the phrase "releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment" of claim 43 should be construed as "at least 80%." PO Resp. 16. Patent Owner notes that this construction would be consistent with our prior constructions of "releases substantially all of said drug after such immersion." Dec. Inst. 6. Petitioner does not object to Patent Owner's proposed construction in its Reply.

Based on the information presented and for the same reasons stated in our Decision to Institute (*id.*), we determine that the broadest reasonable interpretation of "substantially all" as used in the claims is "at least 80%."

B. Principles of Law

To prevail in its challenges to the patentability of the claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

To establish anticipation, each limitation in a claim must be found in a single prior art reference, arranged as recited in the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). While the

limitations must be arranged or combined in the same way as in the claim, identity of terminology is not required. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990). Moreover, a reference anticipates a claim "if it discloses the claimed invention such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995). Thus, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a

reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

C. The Level of Ordinary Skill in the Art

In large part, the parties agree as to the level of ordinary skill in the art. Pet. 10; PO Resp. 10. Both agree that a person of ordinary skill in the art would be a person with a Ph.D. degree in at least pharmaceutical science, chemistry, or chemical engineering along with at least two years of industry experience in the development of controlled-release oral dosage forms. Pet. 10; PO Resp. 10. Both also agree that a person of ordinary skill in the art may have an equivalent level of skill through similar education, training, and industry experience. Pet. 10; PO Resp. 10. In light of the parties' agreement, we adopt that description of the level of ordinary skill in the art for purposes of this proceeding.

D. Anticipation by the '803 Patent

Petitioner asserts that claims 43, 54, 55, 57, 58, and 66 of the '475 patent are anticipated by the '803 patent. Pet. 19–25; Pet. Reply 2–4. Petitioner relies on the Declaration of Dr. Roland Bodmeier. Ex. 1012 ¶¶ 80–94. Patent Owner disagrees with Petitioner's assertions (PO Resp. 27–30), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 94–101, 156–60).

1. The '803 Patent (Ex. 1005)

The '803 patent relates to a drug dosage form adapted for retention in the stomach to deliver a drug over a sustained period of time. Ex. 1005, 1:10-14. The dosage form includes a drug and a polymer matrix formed of a

swellable, water-soluble polymer that expands when contacted with fluids in the stomach, and a rigid or semi-rigid band of insoluble material in which swelling of the water-soluble polymer is constrained. *Id.* at 5:12-18. The insoluble band "facilitates the dosage form remaining in the stomach of a subject over a prolonged period of time." *Id.* at 5:18-21. The insoluble band also prolongs the period of time that the polymer matrix "retains its integrity in an expanded state." *Id.* at 5:28-30. It is thought that the band "reduces the rate of erosion of the polymer matrix, thus maintaining a larger effective size of the dosage form and reducing the chance for its expulsion from the stomach, for a longer period of time than would otherwise occur if the band was not present." *Id.* at 14:33-40. As the dosage form erodes in the stomach or as the active agent diffuses from the matrix, active agent will be released and absorbed in either the stomach or small intestine. *Id.* at 5:38-42.

2. Analysis

As an initial matter, Patent Owner argues that the '803 patent is not prior art under 35 U.S.C. § 102(e) because the '475 patent claims priority to U.S. Patent Application No. 08/870,509 ("the '509 application"), which was filed on June 6, 1997. PO Resp. 19–20. Petitioner disagrees, stating the method claims of the '475 patent were added in a later continuation-in-part application filed March 29, 1999, and are therefore not entitled to the benefit of the June 6, 1997, filing date of the '509 application. Pet. Reply 1–2. At oral argument, Patent Owner conceded this point. Tr. 75:15–21 (stating "I believe we agree [the method claims are] entitled to a 1999 date"). Accordingly, we determine that the '803 patent is prior art to the method claims at issue in this proceeding.

Petitioner contends that independent claim 43 and its dependent claims 54, 55, 57, 58, and 66 are anticipated by the '803 patent. Pet. 19–25. Petitioner asserts, for example, that the '803 patent teaches the limitation of "remains substantially intact until all of said drug is released" in teaching that the addition of an "insoluble material or band (or bands if more than one band is utilized) prolongs the period of time in which the polymer matrix retains its integrity in an expanded state and increases the residence time of the dosage form in the stomach." *Id.* at 22. Petitioner also argues that the '803 patent teaches the use of poly(ethylene) oxide ("PEO") and various other types of highly viscous polymers that "will create formulations that will remain intact." *Id.* at 22–23 (citing Ex. 1012 ¶ 88).

Patent Owner argues that the '803 patent does not disclose the "substantially intact" limitation because it expressly states that the polymer matrix erodes significantly. PO Resp. 27. For example, the '803 patent states that "[e]rosion of the matrix will continue to deliver active agent to the stomach until the matrix has *substantially eroded* so that no significant amount of active agent remains." *Id.* at 27–28 (quoting Ex. 1005, 16:14–19).

We are not persuaded that Petitioner has established by a preponderance of the evidence that the '803 patent teaches the "substantially intact" limitation of claim 43. We construed "substantially intact" to mean "a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles."

Petitioner argues that the '803 patent teaches that its formulations substantially maintain their size and shape until all the drug is released,

stating "the active agent dosage form comprises . . . solid active agent in a gel-forming, erodible polymer matrix having a first portion that swells in the stomach while maintaining its physical integrity for a prolonged period of time." Pet. Reply 2 (quoting Ex. 1005, 7:16–20). Petitioner reasons that even though erosion occurs over time, "the polymer matrix maintains its physical integrity for a prolonged period." *Id.*

Patent Owner argues that the '803 patent does not anticipate the "substantially intact" limitation of claim 43 because it discloses several embodiments that "*erode significantly* such that nearly all of the polymeric matrix has eroded by the final stage of drug release." PO Resp. 27–28 (citing Ex. 1005, 14:19–22, 14:36–40, 16:14–19, Figs. 2–4). While we agree with Patent Owner's characterization of those specific embodiments, that does not preclude Petitioner from showing that the '803 patent teaches the limitation expressly or inherently. We find, however, that Petitioner has not made this showing.

Under claim 43, a dosage form must remain substantially intact "until all of said drug is released." Even if "maintain[ing] its physical integrity" did disclose a dosage form that remains "substantially intact," Petitioner has not shown that maintaining the physical integrity of the dosage form for a "prolonged period of time" expressly or inherently discloses doing so "until all of said drug is released." In other words, a "prolonged period of time" is not necessarily the same as the time period within which "all of said drug is

released."[8] Thus, we are not persuaded that Petitioner has established that the '803 patent discloses the "substantially intact" limitation of claim 43.

Accordingly, after considering the parties' arguments and evidence, we determine that Petitioner has not shown by a preponderance of the evidence that the '803 patent anticipates claims 43, 54, 55, 57, 58, and 66 of the '475 patent.

E. Obviousness over the '837 Patent, Baveja, and Colombo

Petitioner asserts that claims 43, 57, 58, and 66 of the '475 patent are unpatentable as obvious over the '837 patent, Baveja, and Colombo. Pet. 25–41, 43; Pet. Reply 2–4. Petitioner relies on the Declaration of Dr. Bodmeier. Ex. 1012 ¶¶ 95–103, 110. Patent Owner disagrees with Petitioner's assertions (PO Resp. 30–38), relying on the Declaration of Dr. Hopfenberg (Ex. 2010 ¶¶ 162–75).

1. The '837 Patent (Ex. 1006)

The '837 patent relates to the field of alkyl-substituted cellulose-based sustained-release drug dosage forms. Ex. 1006, 1:17–19. Specifically, the dosage form disclosed in the '837 patent comprises a plurality of solid particles of a drug dispersed within a non-crosslinked alkyl-substituted cellulose that "swells unrestricted dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote gastric retention of the pellets in fed-mode induced patients." *Id.* at 1:58–65. The '837 patent teaches that the particles will normally swell to a size of about 6 to 18 mm. *Id.* at 5:8–12. According to the '837 patent specification, the

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[8] This is true under Petitioner's proposed construction of "until all of said drug is released" and under our final construction of the phrase.

dosage form is particularly useful for delivering drugs in a sustained manner within the stomach. *Id.* at 2:39–43.

The '837 patent also discloses drug release experiments using drug dosage forms comprised of hydroxypropylcellulose ("HPC") and aspirin ("ASA"). *Id.* at 7:25–57. The results of the drug release experiments, which were performed in simulated gastric fluid, are shown in Figure 1, which is reproduced below.

Fig. 1

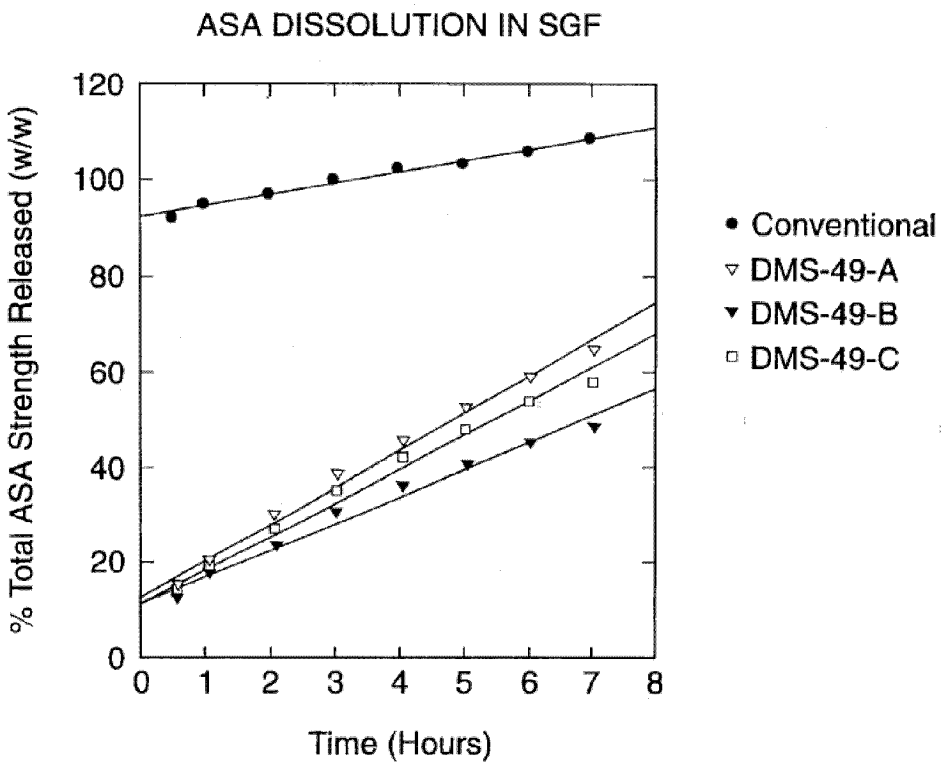

Figure 1 depicts the percentage of aspirin released over time for the various drug formulations tested, including conventional aspirin without HPC. *Id.* at 7:47–52. The release of aspirin was measured at various intervals up to seven hours. *Id.*

2. Baveja (Ex. 1013)

Baveja discloses a dosage form comprised of a swellable hydrophilic matrix that exhibits zero-order (i.e., constant) release of a drug. Ex. 1013, Summary. Baveja uses β-adrenergic blockers propranolol hydrochloride, alprenolol hydrochloride, and metoprolol tartrate as model drugs. *Id.* at 40. Baveja describes tablets with different ratios of HPMC, sodium carboxymethylcellulose ("Na CMC"), and drug, which are then subjected to an in vitro dissolution study. The in vitro dissolution study involves placing the tablets into a dissolution rate test apparatus with diluted HCl (pH 3.0) for three hours and then in 0.2 M phosphate buffer (pH 7.4) for another 9 hours. *Id.*

The results of the dissolution studies for tablets formed from just HPMC and drug are shown in Figures 1–3. For example, Figure 2 is reproduced below:

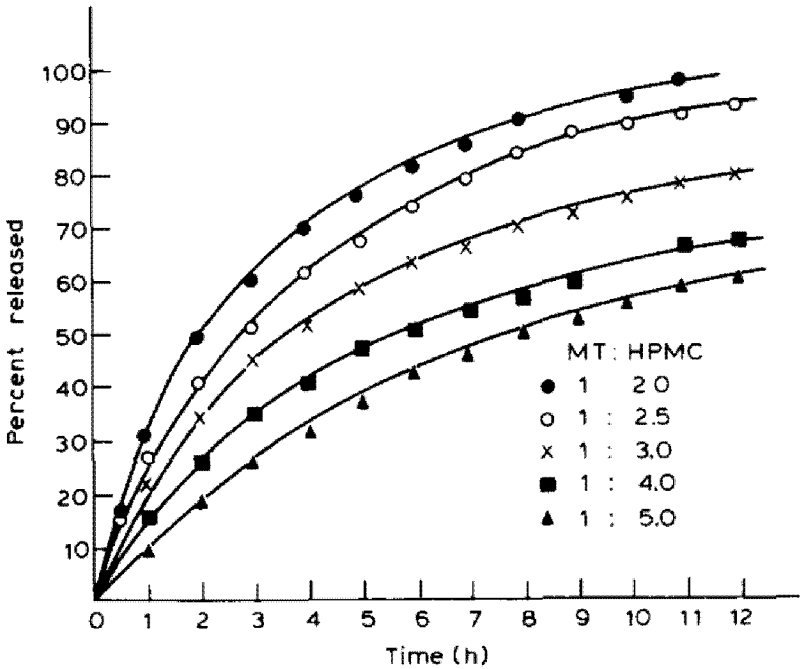

Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

Figure 2 illustrates the cumulative percent of metoprolol tartrate released as a function of time from tablets containing metoprolol tartrate and HPMC in the ratios shown. *Id.* at 41.

As explained by Baveja, the rate of release of the tablets made of drug and HPMC decreases with time, which may be due to "an increase in diffusional path length for the drug[,] which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer." *Id.*

Baveja also describes tablets formed from HPMC, Na CMC, and drug in varying amounts that exhibit a nearly zero-order rate of release. *Id.*, Abstract.

3. Colombo (Ex. 1014)

Colombo relates to swellable matrix systems in the form of a tablet comprising a mixture of the drug diltiazem, HPMC, ethylcellulose, and mannitol. Ex. 1014, 44. Colombo discloses three different matrices: Case 0, the plain matrix; Case 1, the matrix coated with cellulose acetate propionate ("CAP") on one face; and Case 2, the matrix coated with CAP on both faces. *Id.* Colombo describes "[s]welling and release experiments" in which the matrices were swollen in deionized water for 120 minutes, and the drug release measurements were obtained concomitantly with the matrix swelling observations. *Id.*

Colombo describes and depicts the morphological changes in the matrices over time, observing that, in the uncoated system (Case 0), "[v]ery quickly (after 15 min) the swelling of the matrix moves both in axial and radial directions." *Id.* Colombo also discloses the drug release profiles of the systems. *Id.* at 45. Figure 5 of Colombo is reproduced below:

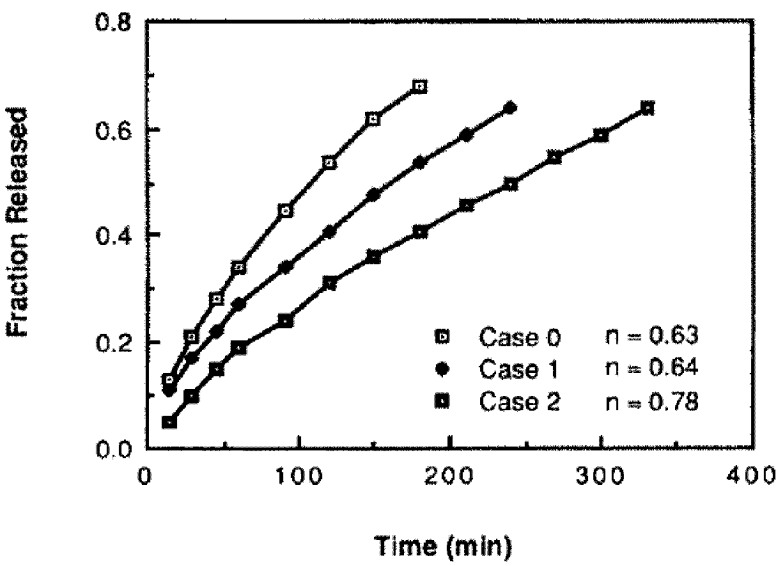

Fig. 5. Drug release profiles of the systems. Calculated values of exponent *n* of Eqn 2 are also shown.

Figure 5 depicts the fraction of diltiazem released over time for the Case 0, Case 1, and Case 2 matrices.

4. Analysis

Petitioner asserts that claims 43, 57, 58, and 66 of the '475 patent are unpatentable as obvious over the '837 patent, Baveja, and Colombo. Petitioner argues that Colombo and Baveja each "disclose every limitation set forth in claim 43 except for the method of administration, which is expressly disclosed by the '837 patent." Pet. 41. Petitioner further contends that a person of ordinary skill in the art would have been motivated to combine the teachings of the '837 patent with Baveja and Colombo given the nature of the problem to be solved and the interrelated teachings of the art. *Id.* at 40.

Looking first at the limitations that Petitioner contends are expressly disclosed, Patent Owner disagrees with Petitioner's contentions, arguing that Baveja does not disclose, either expressly or inherently, drug release by "dissolution and diffusion." PO Resp. 30. Indeed, Patent Owner contends that Baveja actually teaches away from drug release by dissolution and diffusion because it describes the dosage form relied upon by Petitioner as having a "major disadvantage" because it does not exhibit zero-order release. *Id.* at 23. We find, however, that Baveja teaches "dissolution and diffusion" expressly when it states that "Figs. 1–3 reveal that the rate of release decreased with time and this may be due to an increase in diffusional path length for the drug which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer." Ex. 1013, 41. Moreover, the fact that Baveja may prefer dosage forms that exhibit zero-order release, over those that do not, does not teach

away from the claimed invention. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("This court has further explained that just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

For the remaining limitations of claim 43 that Petitioner contends are expressly disclosed, based on the evidence presented, we are persuaded that Petitioner has established that Baveja teaches those limitations expressly. Pet. 29–33; Ex. 1012 ¶¶ 98–103. We further agree with Petitioner that Baveja does not expressly disclose a matrix that "swells upon the imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode" (i.e. the "swelling" limitation) and that "remains substantially intact until all of said drug is released" (i.e., the "substantially intact" limitation). *See* Pet. 30–33.

Petitioner, however, asserts that Baveja inherently teaches the "swelling" limitation and the "substantially intact" limitation. Pet. 30–32 . To prove inherency, Petitioner must establish that "the missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). We are not persuaded that Petitioner has met this test for either limitation.

Regarding the "swelling" limitation, Petitioner asserts that Baveja discloses a tablet that is 11 mm in diameter prior to imbibition of water and uses HPMC that is a water soluble, swellable polymer. Pet. 30 (citing Ex. 1012 ¶ 102); *see* Ex. 1013, Abstract, 40. Petitioner also relies on the test results from Dr. Kinam Park, which allegedly "confirm that Baveja's formulations swell to a size of about 13.5–14.5 mm after immersion in [simulated gastric fluid]." Pet. 30 (citing Ex. 1016, Ex. 1012 ¶ 102).

Petitioner asserts that Baveja inherently discloses the "swelling" limitation because "[s]welling of a tablet of the size described in Baveja . . . will promote retention in the stomach during the fed mode." *Id.* Petitioner bases its argument in part on the '475 patent Specification's disclosure regarding tablet size. *Id.* at 31 (citing Ex. 1012 ¶ 53). Although Baveja does disclose a "swelling front" (Ex. 1013, 41), we are not persuaded that Petitioner has shown sufficiently that Baveja inherently teaches the entirety of the "swelling" limitation. Specifically, we are not persuaded that Petitioner has shown that Baveja necessarily teaches swelling that "will promote retention in the stomach during the fed mode." For example, it is not clear whether having a tablet that is 11 mm in size in diameter (without knowing any other dimension of the tablet) will necessarily remain in the stomach.

As for the "substantially intact" limitation, Petitioner argues that Baveja's formulation inherently would remain substantially intact. Pet. 32. As support, Petitioner relies on both the testimony of Dr. Bodmeier and the test results of Dr. Kinam Park. *Id.* According to Petitioner, Dr. Park re-created two formulations in Baveja to determine the release kinetics and swelling properties of the dosage forms. Pet. 33–39. Because Dr. Park did not provide evidence of a positive control, however, we cannot conclude with sufficient certainty that Dr. Park's dosage forms were, in fact, the same dosage forms disclosed by Baveja. During oral argument, Petitioner accepted our finding. Tr. 29:21–22 ("We accept the Board's conclusion regarding the prior test results . . . ."). We also do not give persuasive weight to Dr. Bodmeier's unsupported opinion that the Baveja tablets will remain substantially intact. *See* 37 C.F.R. § 42.65(a) (opinion testimony that does not disclose underlying facts or data "is entitled to little or no weight");

Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294 (Fed. Cir. 1985) (a lack of objective support for expert opinion "may render the testimony of little probative value in a validity determination"). Accordingly, we are not persuaded that Baveja inherently teaches the "substantially intact" limitation.

Similarly, we are not persuaded that Colombo teaches the "swelling" or "substantially intact" limitations, either expressly or inherently. Petitioner asserts that Colombo teaches the "swelling" limitation because it discloses the use of a 7 mm x 2.65 mm tablet prior to imbibition of deionized *water*. Pet. 30 (citing Ex. 1014, 44). The "swelling" limitation of the claims, however, requires "imbibition of *gastric fluid*." Petitioner directs us to no persuasive evidence that Columbo swells by imbibition of gastric fluid, as required by the claims. That is, Petitioner has not established that deionized water is an "artificial fluid[] recognized by those skilled in the art as a suitable model for the fluid of the human stomach," as required by our construction of "gastric fluid." Thus, we are not persuaded that Colombo teaches the "swelling" limitation, either expressly or inherently.

As for the "substantially intact" limitation, Petitioner asserts that Colombo's swelling studies, conducted in water, teach this limitation. Pet. 32. Specifically, Petitioner asserts that the results indicate that the Case 0 formulations "swell significantly and remain substantially intact over the course of at least six hours." *Id.* (citing Ex. 1014, Figs. 1–4; Ex. 1012 ¶ 99). The "substantially intact" limitation, however, requires that the matrix remain substantially intact "until all of said drug is released." We are

not persuaded that Petitioner has shown that Colombo teaches this limitation expressly or inherently.[9]

Petitioner provides, however, an alternative source for teaching these two limitations missing from Baveja and Colombo. Petitioner asserts that the '837 patent discloses expressly the "swelling" and "substantially intact" limitations. Pet. 16–18. We agree. The '837 patent discloses that "swollen particles will be of a size that promotes their retention in the stomach . . . particularly when the patient is in the fed mode." Ex. 1006, 5:9–11. The '837 patent also discloses that because alkyl-substituted celluloses "dissolve very slowly in gastric fluid, the particles maintain their integrity over at least a substantial portion (i.e., at least about 90% and preferably over 100% of the intended dosing period)." *Id.* at 4:42–46.

We are persuaded, therefore, that Petitioner has established that each limitation of claim 43 was known in the art, as evidenced by the teachings of Baveja, Colombo, and the '837 patent. A patent, however, "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Petitioner must also show that there was a reason to combine those elements to achieve the claimed invention with a reasonable expectation of success. *See PAR Pharm.*, 773 F.3d at 1193. To make that determination, we can look to "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background

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[9] Of note, we are also not persuaded that Colombo teaches releasing "substantially all of said drug within about ten hours after such immersion." Figure 5 of Colombo, cited by Petitioner, does not show any formulation that ever releases at least 80% of the drug. Ex. 1014, Fig. 5.

knowledge possessed by a person having ordinary skill in the art." *Id.* We can also look to the nature of the problem to be solved. *In re Gartside*, 203 F.3d 1305, 1319 (Fed. Cir. 2000) (holding that suggestion to combine "may come from, *inter alia*, the teachings of the references themselves and, in some cases, from the nature of the problem to be solved"). After considering the parties' arguments and evidence, however, we are not persuaded that Petitioner has established that a person of ordinary skill would have combined the teachings in the manner contended by Petitioner.

Petitioner argues that a person of ordinary skill in the art would have been led to combine the teachings of Baveja, Colombo, and the '837 patent for several reasons. Pet. 38. First, Petitioner argues that a person of ordinary skill in the art would have had a reason to combine Baveja, Colombo, and the '837 patent given the nature of the problem to be solved: "to formulate a swellable, controlled release oral dosage form for releasing a drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." *Id.* at 40.

Second, Petitioner argues that the references have interrelated teachings. According to Petitioner, each of the references is directed to controlled-release dosage forms that contain HPMC with similar drug-to-polymer weight ratios. *Id.*; Ex. 1012 ¶¶ 101–02. For example, Baveja's matrix contains a drug-to-polymer ratio that falls within the weight ratio range disclosed by the '837 patent. Pet. 40 (citing Ex. 1013, Figs. 1 and 2 and Ex. 1014, 44); Ex. 1012 ¶ 121. Moreover, Petitioner argues that "Baveja and Colombo (1990) both teach oral dosage forms formulated with drugs that have at least one ionized group within the pH range 5–8, including alprenolol HCl (Ex. 1013) and diltiazem HCl (Ex. 1014)." Pet. 40.

Petitioner then concludes that "it would be natural for a [person of ordinary skill in the art] to combine the teachings of these references." *Id.* at 40–41.

In response, Patent Owner argues that Petitioner has failed to demonstrate a motivation to combine the cited references with a reasonable expectation of success. Patent Owner challenges Dr. Bodmeier's statement that it would be "natural" to combine Baveja, Colombo, and the '837 patent. PO Resp. 36–37. According to Patent Owner, Dr. Bodmeier fails to provide any substantive evidence to support his testimony that it would take him "a week" to come up with the claimed invention. *Id.* at 37 (quoting Ex. 2018, 80:19–81:8). In contrast to Dr. Bodmeier's testimony, Patent Owner notes that Jenny-Louie Helm, an inventor of the '475 patent ("Inventor Helm"), testified that it "took years of research and testing in the laboratory to manipulate different variables, such as type of polymer, molecular weight, particle size, dosage size, matrix chemical structure, and manufacturing processes, to come up with the claimed inventions." *Id.* at 38; Ex. 2016 ¶ 21 (Helm Decl.) ("It took me three years testing various polymers with guidance of Dr. Shell to achieve the Captopril formulation that contained the aspects of the claims of the '475 and '280 Patents."). Consistent with Inventor Helm's testimony, Patent Owner asserts that its declarant, Dr. Hopfenberg, testified that a person of ordinary skill in the art would not have reasonably expected to successfully achieve the claimed invention given that a "vast array of structural considerations affect polymer and matrix properties." PO Resp. 38 (citing Ex. 2010 ¶ 65).

On the record developed at trial, we are not persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reason to combine the references with a

reasonable expectation of success. Although the references may have interrelated teachings, as Petitioner asserts, Petitioner has not explained persuasively *how or why* a person of ordinary skill in the art would have combined the "swelling" and "substantially intact" features of the '837 patent with the dosage formulation of Baveja and Colombo.

In its Reply, Petitioner asserts that "the advantages and techniques of formulating controlled release dosage forms that are retained in the stomach were well-known at the time of the alleged invention." Pet. Reply 11. Petitioner also asserts another reason to combine the cited references:

> A [person of ordinary skill in the art] would look to (1) Baveja to learn how to adjust the rate of drug release by varying the drug-to-polymer (HPMC) weight ratio and (2) either Colombo or the '837 patent for confirmation that the same type of polymer used in Baveja will (a) swell to a size that will promote gastric retention in the fed mode, and (b) remain substantially intact until all of the drug is released.

Pet. Reply 11 (citing Ex. 1012 ¶¶ 101–103). But here, again, Petitioner speaks in generalizations and does not explain persuasively *why* a person of ordinary skill in the art, learning from Baveja how to adjust the rate of drug release by varying the drug-to-polymer weight ratio, would need or want to look to Colombo or the '837 patent "for confirmation" of the "swelling" and "substantially intact" properties. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing district court's judgment of invalidity where expert's testimony "was vague and did not articulate reasons why a person of ordinary skill in the art at the time of the invention would combine these references").

To the extent Petitioner relies on the nature of the problem to be solved to supply the reason for the combination, we remain unpersuaded.

Petitioner's recitation of the nature of the problem to be solved is essentially a recitation of claim 43 itself: "to formulate a swellable, controlled release oral dosage form for releasing a drug with particular release kinetics and that will remain substantially intact and be retained in the stomach during the fed mode." Pet. 40. As our reviewing court has recently reminded us, however, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)). As such, the Federal Circuit stated that when considering the reason to combine, "the problem examined is not the specific problem solved by the invention." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Here, the claim represents the specific problem solved by the invention, rather than the general problem facing the inventors. Thus, we find that by defining the nature of the problem to be solved as the specific problem solved by the invention, Petitioner has relied on impermissible hindsight to supply the reason to combine the references. *See id.* (affirming the district court's recognition that "an overly narrow 'statement of the problem [can] represent[] a form of prohibited reliance on hindsight, [because] [o]ften the inventive contribution lies in defining the problem in a new revelatory way'") (quoting *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (alterations in original)).

Even if we were to find that Petitioner has established that a person of ordinary skill in the art would have had a reason to combine the teachings of Baveja, Colombo, and the '837 patent, we are still not persuaded that

Petitioner has established that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

Petitioner argues that a person of ordinary skill in the art "following logical design preferences and readily available and known options would have necessarily developed a method and controlled-release dosage form that included all recited claim limitations." Pet. 26. For example, Petitioner and its declarant argue that it was known to a person of ordinary skill in the art "how to formulate a dosage form with a swellable, hydrophilic, polymeric matrix that would remain substantially intact until substantially all of the drug is released, like those described and claimed in the '475 patent." *Id.* at 28 (citing Ex. 1012 ¶¶ 54–59).

We are not persuaded that a person of ordinary skill in the art would have had a reasonable expectation of success, in part, because both parties' declarants testified about the number of formulation considerations at play when preparing a drug formulation. For example, Petitioner's declarant testified that there were formulation considerations such as "molecular weight, chemical substitution, particle size, hydration rate effect, polymer content, dosage form, dosage size and manufacturing processes." Ex. 1004 ¶ 37. Similarly, Patent Owner's declarant stated that "[a] person of ordinary skill in the art understands that formulation of a polymer matrix involves a vast array of interacting 'formulation considerations' affecting polymer and matrix properties." Ex. 2010 ¶ 65. Despite this testimony from its own declarant (as confirmed by Patent Owner's declarant), we find that Petitioner does not address sufficiently why a person of ordinary skill in the art would believe it could modify the formulation of Baveja to incorporate the "swelling" and "substantially intact" features of the '837 patent without, for

example, affecting the other properties of the original Baveja formulation (e.g., the drug release profile). Nor has Petitioner identified any combinations of Baveja, Colombo, and the '837 patent that would be most promising to try. As such, we reach the same conclusion as the Federal Circuit in *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013). That is, we find that "[w]ithout a reasonable expectation of success or clues pointing to the most promising combinations, an artisan could have spent years experimenting without success." *Id.*

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 43, 57, 58, and 66 are unpatentable as obvious over the '837 patent, Baveja, and Colombo.

F. Obviousness of Claims 54 and 55 over the '837 Patent, Baveja, Colombo, and the '125 Patent

Petitioner asserts that claims 54 and 55 of the '475 patent—which depend from claim 43—are unpatentable as obvious over the '837 patent, Baveja, Colombo, and the '125 patent. Pet. 41–43; Pet. Reply 12–13. Patent Owner disagrees with Petitioner's assertions. PO Resp. 38–39.

1. The '125 Patent (Ex. 1015)

The '125 patent relates to controlled release tablets comprising a pharmaceutical agent and an excipient, which includes a water-swellable polymer and a lubricant. Ex. 1015, Abstract. The '125 patent teaches that the polymers of choice include uncrosslinked PEO and HPMC, either alone or mixed together. *Id.* at 4:18-30.

The release of drugs from the tablet is dependent upon the relative magnitude of the rate of polymer swelling and the rate of polymer erosion.

Id. at 4:30-34. The '125 patent states that "[i]t is most preferable to attain the synchronization of the velocities of the swelling front and the erosion front in order to achieve zero-order [i.e., constant] release kinetics from hydrophilic polymer matrices." *Id.* at 4:37-41.

2. Analysis

Claims 54 and 55 depend from claim 43 and recite the method of claim 43 where the polymeric matrix comprises PEO at a molecular weight in the range of at least about 4,000,000 (claim 54) or a range of from about 4,500,000 to about 10,000,000 (claim 55). Ex. 1001, 26:52-58. The '125 patent teaches a drug dosage form comprising a drug and PEO having a molecular weight of 5,000,000. Ex. 1015, 12:3-5.

Because claims 54 and 55 depend from claim 43, and Petitioner relies on the same rationale for combining the teachings of the references, we determine for the same reasons stated above that Petitioner has failed to establish that a person of ordinary skill in the art would have had a reason to combine the teachings of the '837 patent, Baveja, Colombo, and the '125 patent to achieve the claimed invention with a reasonable expectation of success.

After considering the parties' arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 54 and 55 are unpatentable as obvious over the '837 patent, Baveja, Colombo, and the '125 patent.

G. Secondary Considerations of Nonobviousness

In light of our determination that Petitioner has not shown by a preponderance of the evidence that any of the challenged claims are

unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

III. MOTIONS TO EXCLUDE EVIDENCE

Both parties filed motions to exclude evidence offered by the other side. The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence ("FRE"). *See* 37 C.F.R. §§ 42.20(c), 42.62(a). We address each party's motion in turn.

1. Petitioner's Motion to Exclude Evidence

Petitioner moves to exclude portions of Dr. Hopfenberg's declaration and a claim chart for Gralise® (Ex. 2013) as improperly incorporated by reference and as irrelevant because they are improperly incorporated. Paper 40, 3–5. We decline to do so. As explained in our prior Order (Paper 29), to the extent any such violations have occurred, we have not considered such evidence in reaching our decision. Therefore, we dismiss Petitioner's motion as moot.

Petitioner also moves to exclude certain testimony of Inventor Helm. Paper 40, 10–13. We decline to do so. To the extent we have relied on the testimony of Inventor Helm, that testimony was based on her own work. *See* Ex. 2016 ¶ 21 (testifying how long it took her to develop an embodiment of the claims). Such testimony based on her own personal knowledge is relevant and proper lay witness testimony under FRE 701, 602, and 401/402/403. Accordingly, we deny Petitioner's motion as to this evidence.

Petitioner also moves to exclude certain evidence relating to Patent Owner's assertions of commercial success, licensing, long-felt but unmet need, and unexpected results. Paper 40, 5–15. Given our determination that

we need not reach Patent Owner's evidence of secondary considerations, we need not reach the merits of Petitioner's Motion to Exclude.

2. Patent Owner's Motion to Exclude Evidence

Patent Owner also moves to exclude (1) Exhibits 1055, 1056, and 1065 (Paper 47, 1–8); (2) Exhibit 1071 and the related testimony of Dr. Bodmeier (*id.* at 8–10); and (3) portions of the cross-examination testimony of Dr. Eric Gaier (*id.* at 11–13). Because we did not rely on any of these exhibits or testimony in reaching our Decision here, we dismiss Patent Owner's motion to exclude this evidence as moot.

IV. CONCLUSION

We conclude that Petitioner has not shown by a preponderance of the evidence that claims 43, 54, 55, 57, 58, and 66 of the '475 patent are unpatentable under 35 US.C. §§ 102 or 103.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 43, 54, 55, 57, 58, and 66 of the '475 patent are not held unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is *denied in part and otherwise dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *denied in part and otherwise dismissed*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2014-00379
Patent 6,340,475 B2

PETITIONER:

Gasper J. LaRosa
gjlarosa@jonesday.com

Kelsey I. Nix
knix@jonesday.com

Lynda Q. Nguyen
lqnguyen@jonesday.com

PATENT OWNER:

Judy M. Mohr
JMohr@MWE.com

Paul Andre
PAndre@kramerlevin.com

Geoffrey G. Hu
GHu@kramerlevin.com

US006635280B2

(12) **United States Patent**
Shell et al.

(10) **Patent No.: US 6,635,280 B2**
(45) **Date of Patent: *Oct. 21, 2003**

(54) **EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE**

(75) Inventors: **John W. Shell**, Hillsborough, CA (US); **Jenny Louie-Helm**, Union City, CA (US); **Micheline Markey**, Santa Cruz, CA (US)

(73) Assignee: **DepoMed, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/045,823**

(22) Filed: **Nov. 6, 2001**

(65) **Prior Publication Data**

US 2003/0039688 A1 Feb. 27, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/282,233, filed on Mar. 29, 1999, now Pat. No. 6,340,475, which is a continuation-in-part of application No. 08/870,509, filed on Jun. 6, 1997, now abandoned.

(51) **Int. Cl.**[7] **A61K 9/26**; A61K 9/14

(52) **U.S. Cl.** **424/469**; 424/464; 424/468; 424/488; 424/486; 424/487

(58) **Field of Search** 424/469, 464, 424/468, 488, 486, 487

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WO	WO 98/55107	12/1998

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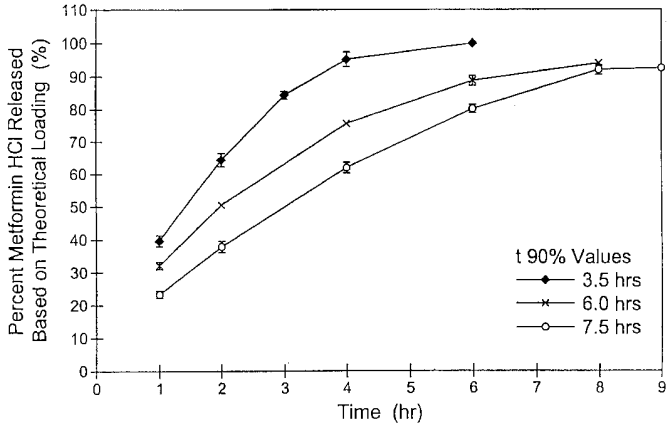
Primary Examiner—Thurman K. Page
Assistant Examiner—Rachel M. Bennett
(74) *Attorney, Agent, or Firm*—M. Henry Heines; Townsend and Townsend and Crew, LLP

(57) **ABSTRACT**

Drugs are formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic polymers that swell upon imbibition of water to a size that is large enough to promote retention of the dosage form in the stomach during the fed mode. The oral formulation is designed for gastric retention and controlled delivery of an incorporated drug into the gastric cavity, and thus administered, the drug is released from the matrix into the gastric fluid by solution diffusion. The swollen polymeric matrix, having achieved sufficient size, remains in the gastric cavity for several hours if administered while the patient is in the fed mode, and remains intact long enough for substantially all of the drug to be released before substantial dissolution of the matrix occurs. The swelling matrix lowers the accessibility of the gastric fluid to the drug and thereby reduces the drug release rate. This process, together with diffusion retardation by selection of specific polymers, polymer molecular weights, and other variables, results in a sustained and controlled delivery rate of the drug to the gastric cavity.

70 Claims, 9 Drawing Sheets



Purdue Exhibit 1001

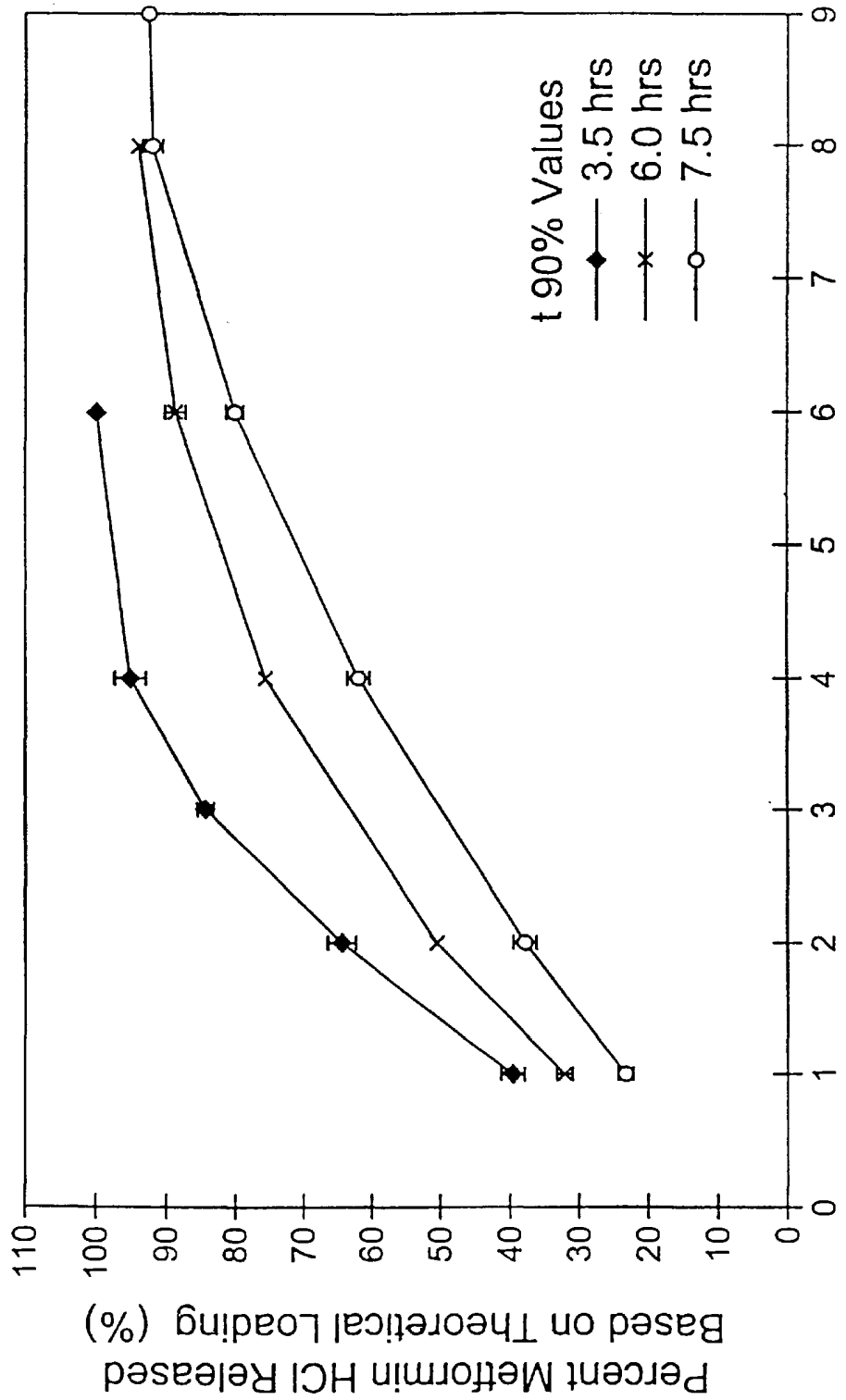

Percent Metformin HCl Released
Based on Theoretical Loading (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (hr)
t 90% Values
3.5 hrs
6.0 hrs
7.5 hrs

Fig. 1

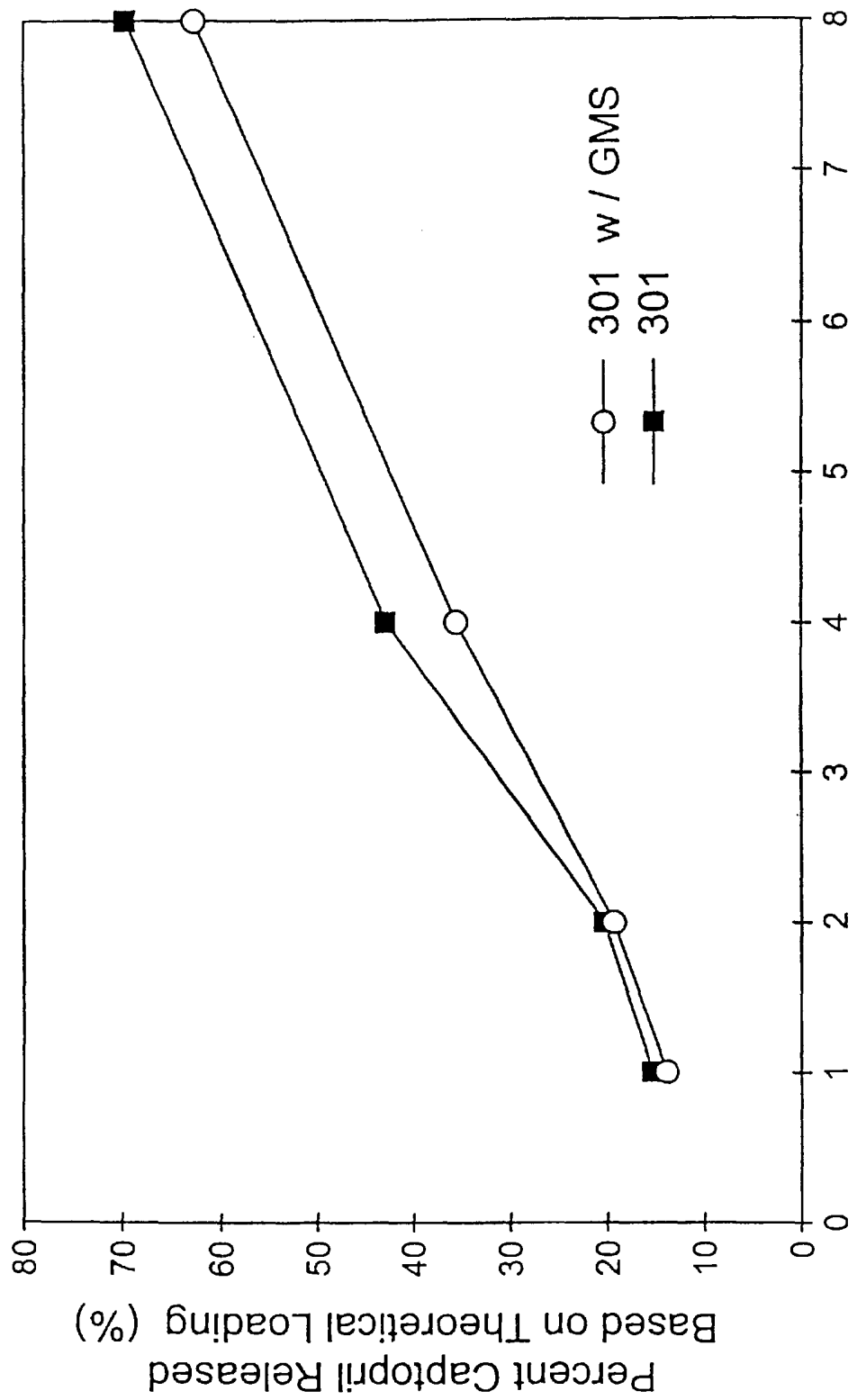

Percent Captopril Released
Based on Theoretical Loading (%)
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hr)
301 w / GMS
301

Fig. 2

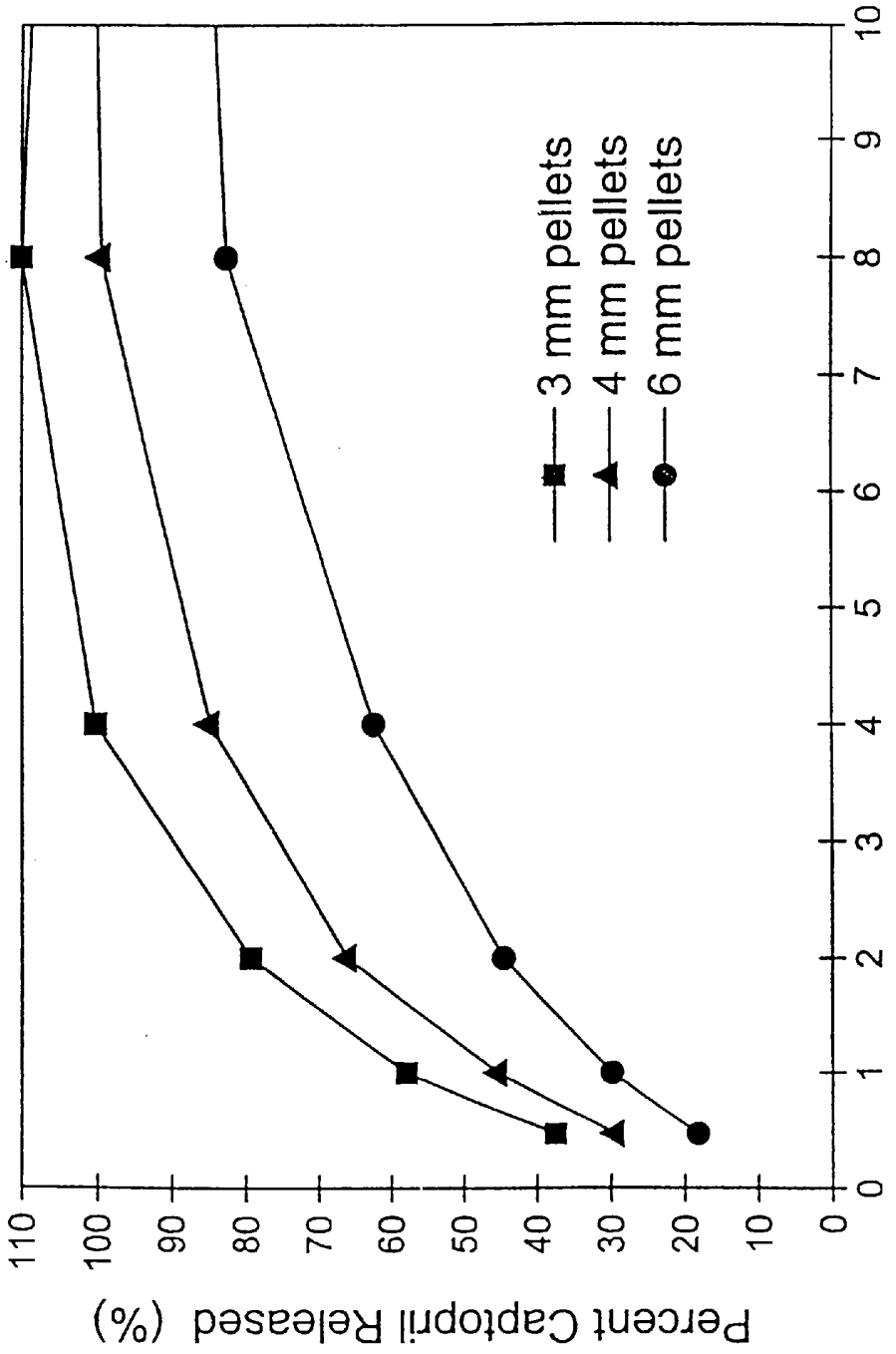

Percent Captopril Released (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)
3 mm pellets
4 mm pellets
6 mm pellets

Fig. 3

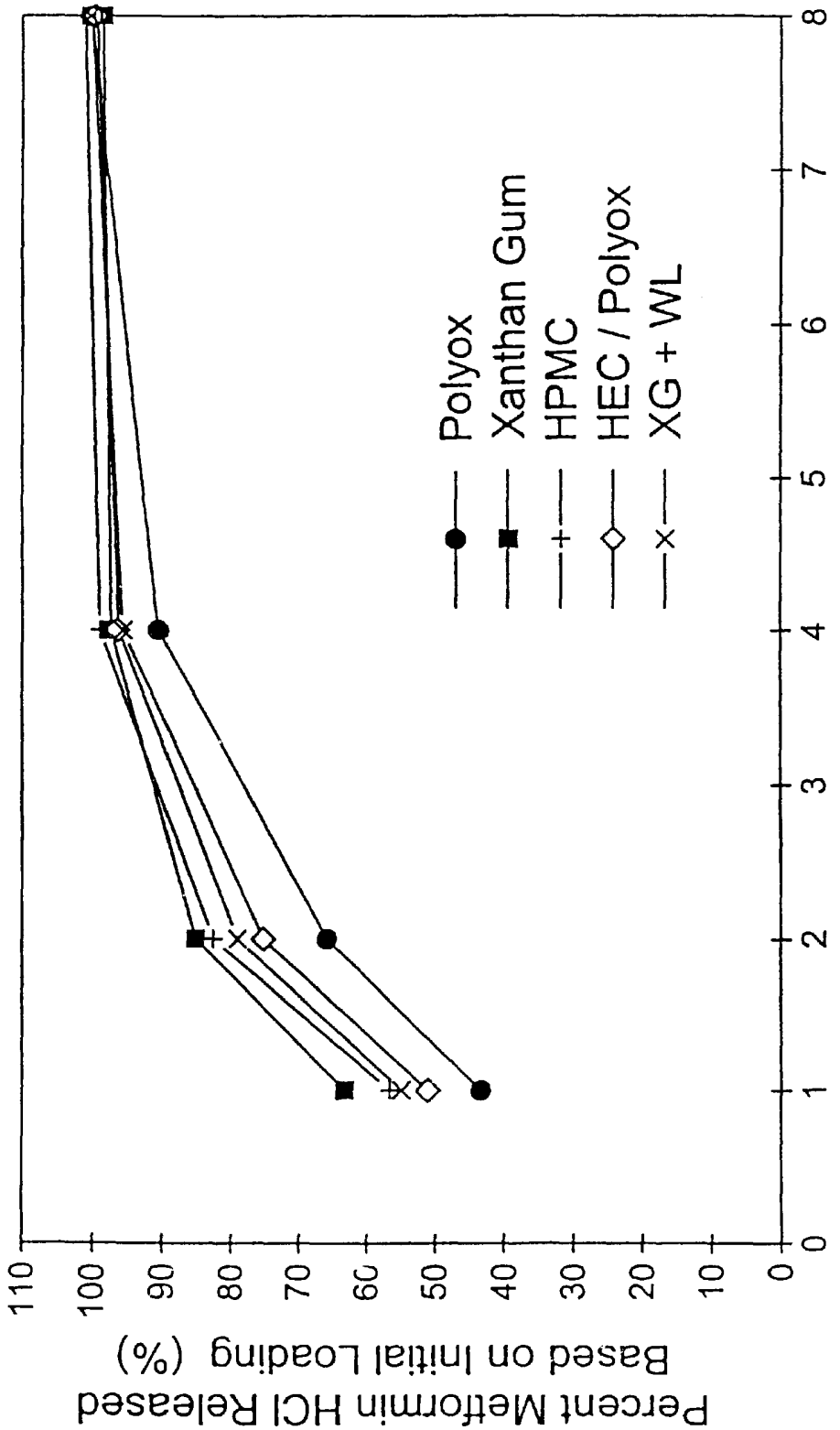

Percent Metformin HCl Released
Based on Initial Loading (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hr)
Polyox
Xanthan Gum
HPMC
HEC / Polyox
XG + WL

Fig. 4

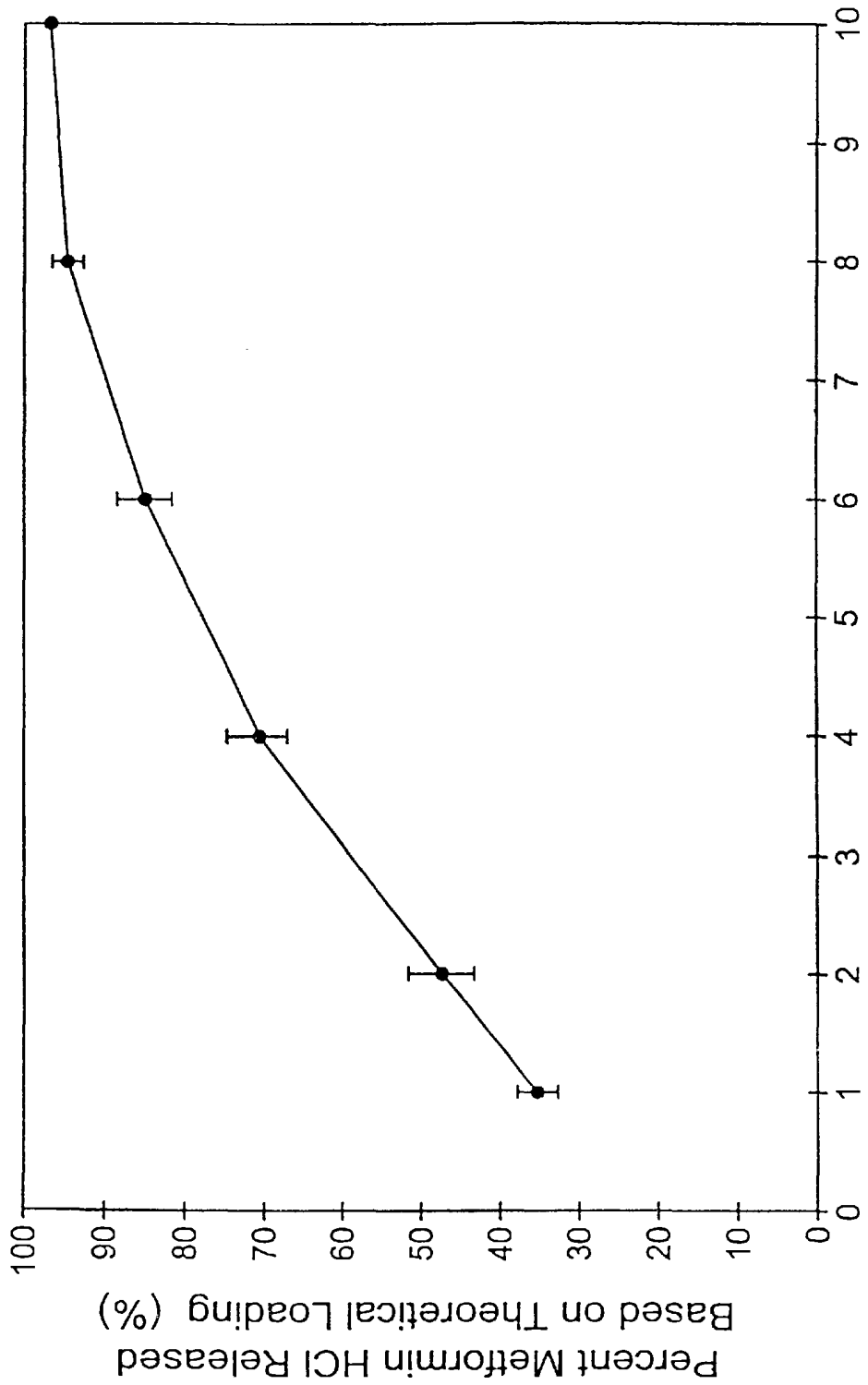

Percent Metformin HCl Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)

Fig. 5

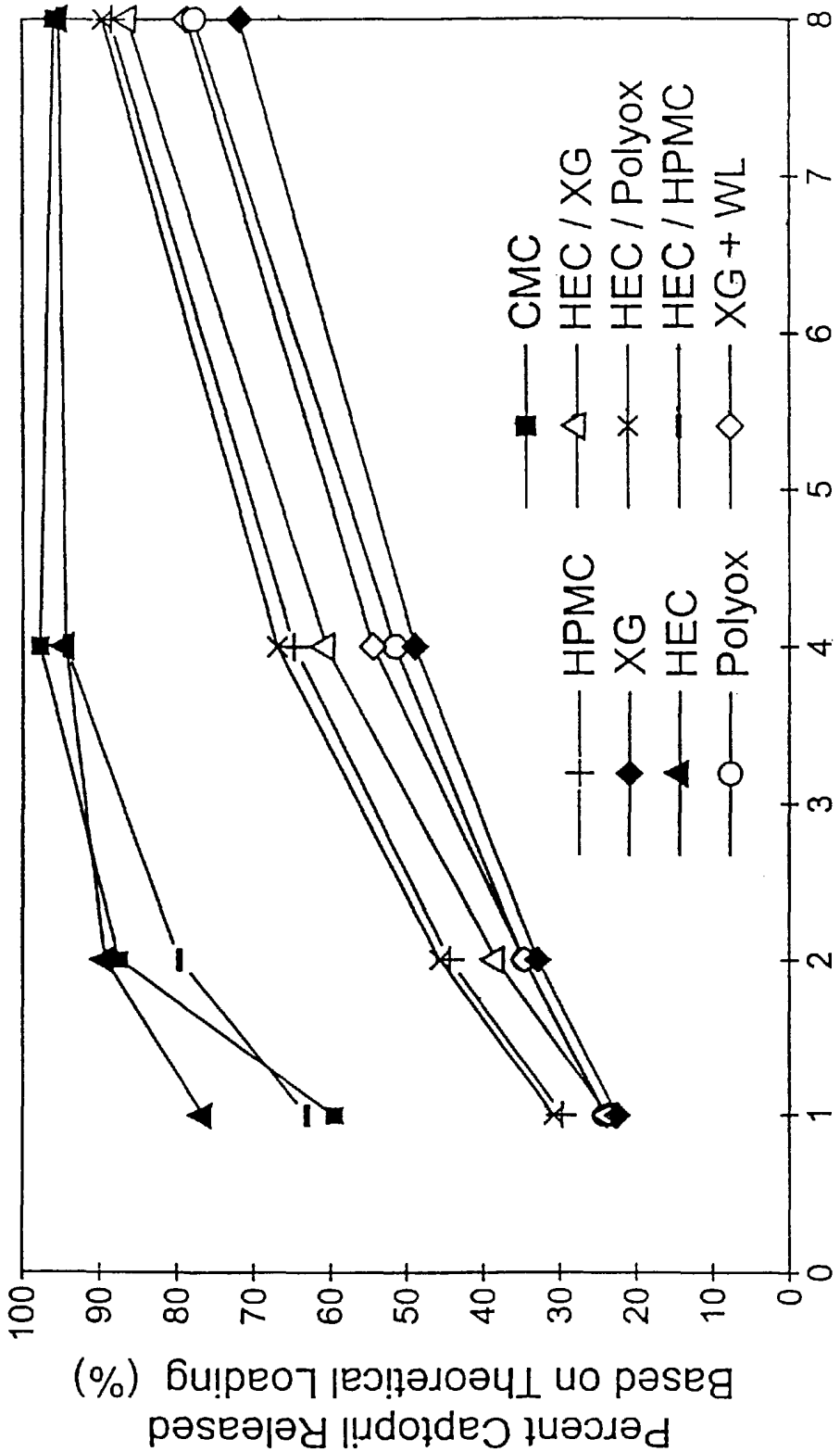

Percent Captopril Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hr)
CMC
HEC / XG
HEC / Polyox
HEC / HPMC
XG + WL
HPMC
XG
HEC
Polyox

Fig. 6

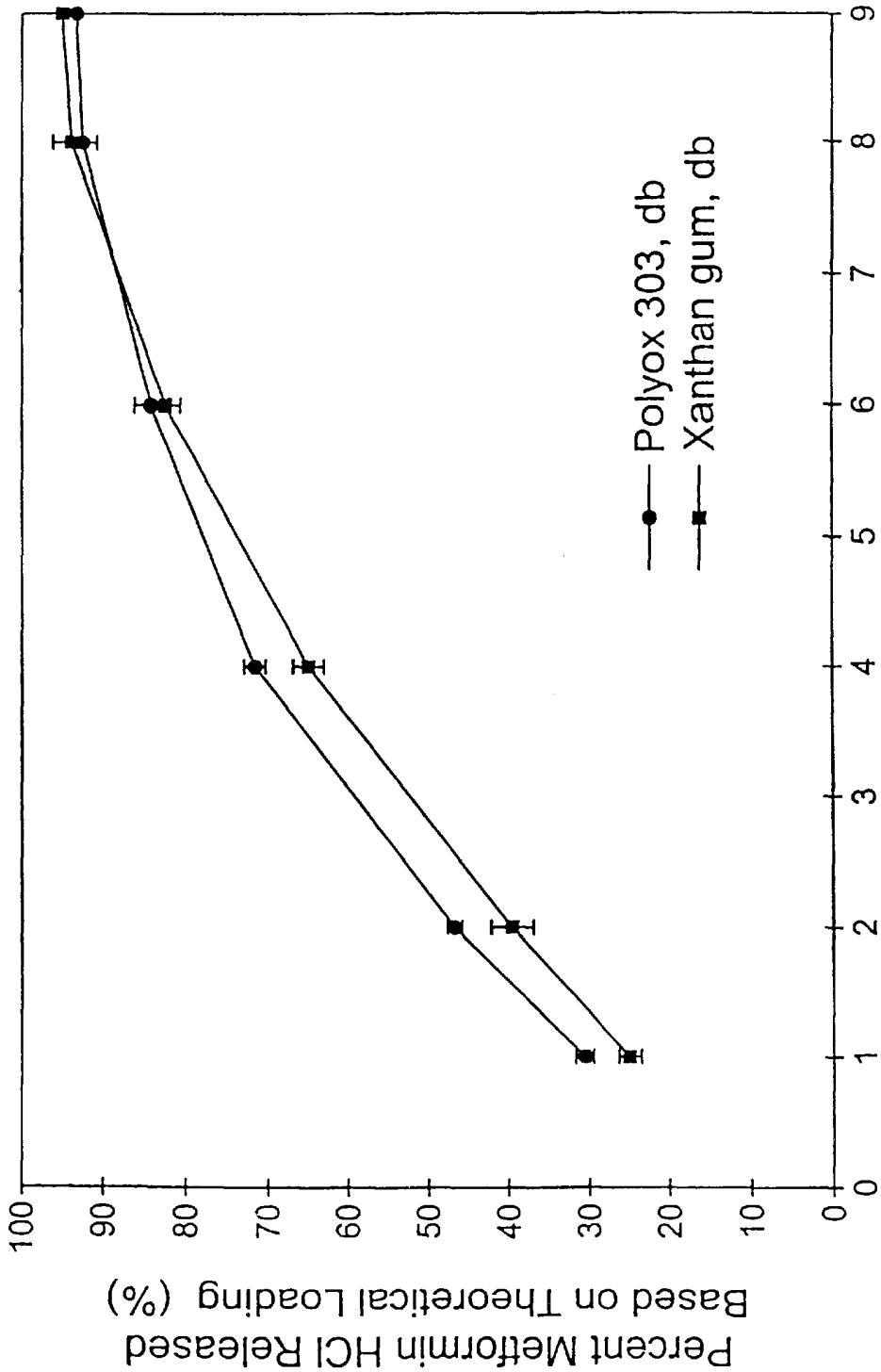

Percent Metformin HCl Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (hr)
Polyox 303, db
Xanthan gum, db

Fig. 7

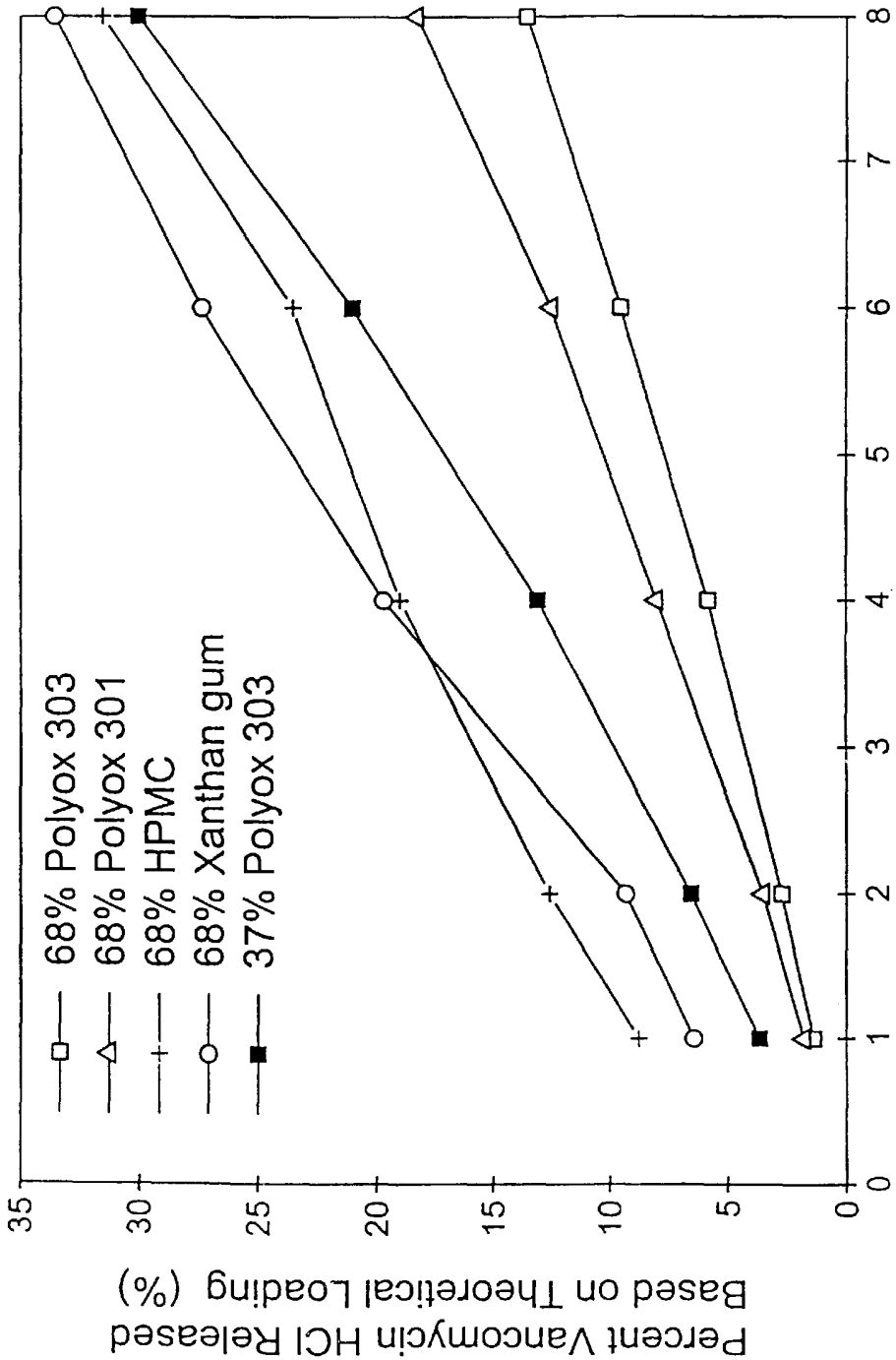

Percent Vancomycin HCl Released
Based on Theoretical Loading (%)
0
5
10
15
20
25
30
35
0
1
2
3
4
5
6
7
8
Time (hr)
68% Polyox 303
68% Polyox 301
68% HPMC
68% Xanthan gum
37% Polyox 303

Fig. 8

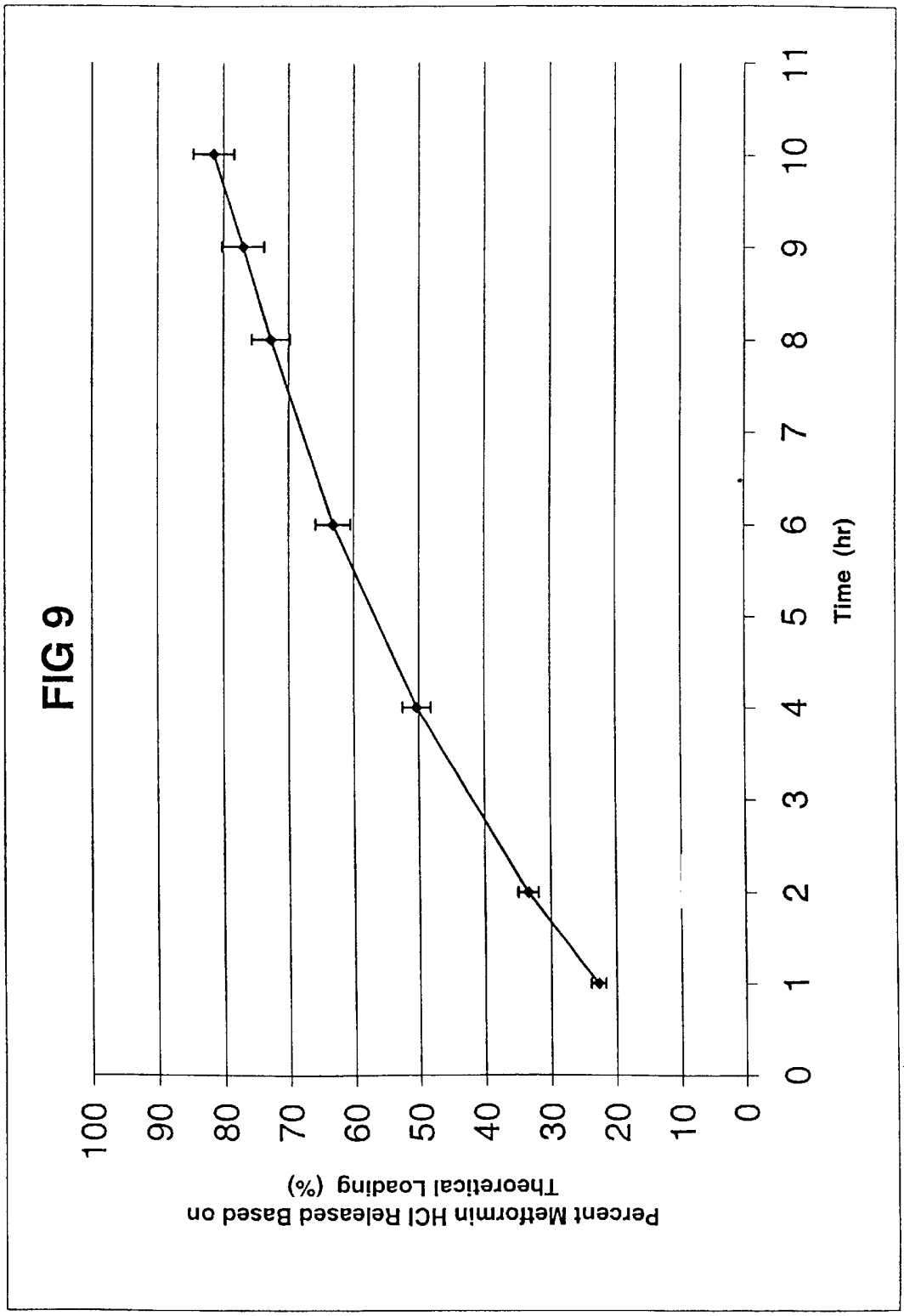

Percent Metformin HCl Released Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11
Time (hr)

FIG 9

EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a con. of Ser. No. 09/282,253 filed Mar. 29, 1999, now U.S. Pat. No. 6,340,475, which is a continuation-in-part of application Ser. No. 08/870,509, filed Jun. 6, 1997, now abn the entire contents of which are hereby incorporated herein by reference.

This invention is in the general field of pharmacology, and relates in particular to formulations for drugs that benefit from a prolonged time of controlled release in the stomach and upper gastrointestinal (GI) tract, and from an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. One goal in this invention is to release highly soluble drugs in a controlled manner over an extended period of time. Another goal is to extend the time of delivery into the stomach of drugs that are preferentially absorbed high in the GI tract, for purposes of achieving a greater and more prolonged therapeutic effect and thus reducing the frequency of administration required; a more efficient use of the drugs; and a more effective treatment of local stomach disorders. Another goal is to minimize both lower-tract inactivation of the drug and drug effects on the lower intestinal flora by confining the delivery and absorption of the drug to the upper GI tract.

BACKGROUND OF THE INVENTION

Drugs that are administered in the form of conventional tablets or capsules become available to body fluids at a rate that is initially very high, followed by a rapid decline. For many drugs, this delivery pattern results in a transient overdose, followed by a long period of underdosing. This is a pattern of limited clinical usefulness. The delivery pattern was improved in the 1970's with the introduction of a variety of controlled delivery systems. By providing relatively constant, controlled drug delivery, these systems avoided the overdose and the underdose effects. These improvements provided effective medication with reduced side effects, and achieved these results with reduced dosing frequency.

Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrices do not provide adequate control over the drug release rate, instead resulting in a release that approximates first-order kinetics. That is, the rate of release is an inverse function of the square root of the elapsed time. With this pattern of release, most of the drug in the matrix is often released within the first hour in an aqueous medium.

One method of prolonging the release of a highly water-soluble drug is disclosed in International Patent Application Publication No. WO 96/26718, published Sep. 6, 1996 (applicant: Temple University; inventor: Kim). The method of this publication is the incorporation of the drug into a polymeric matrix to form a tablet that is administered orally. The polymer is water-swellable yet erodible in gastric fluids, and the polymer and the proportion of drug to polymer are chosen such that:

(i) the rate at which the polymer swells is equal to the rate at which the polymer erodes, so that the swelling of the polymer is continuously held in check by the erosion, and zero-order release kinetics (constant delivery rate) of the drug from the matrix are maintained;

(ii) the release of drug from the matrix is sustained over the full erosion period of the polymer, the tablet therefore reaching complete solution at the same time that the last of the drug is released; and

(iii) release of the drug from the matrix will be extended over a period of 24 hours.

A key disclosure in WO 96/26718 is that to achieve the release of drug in this manner requires the use of a low molecular weight polymer. If, by contrast, a high molecular weight polymer is used and the swelling rate substantially exceeds the erosion rate, the lack of erosion will prolong even further the delivery of the drug residing close to the center of the tablet and even prevent it from being released. Thus, there is no disclosure in WO 96/26718 that a drug of high water solubility can be released from a high molecular weight polymer in a period of time substantially less than 24 hours, or that any advantage can be obtained by the use of a polymer that does not erode as quickly as it swells. This failure is particularly significant since even swollen tablets will not remain in the stomach beyond the duration of the fed mode, which typically lasts for only 4 to 6 hours.

For drugs of any level of solubility, the retention of the drug in a tablet or other dosage form beyond the duration of the fed mode raises a number of problems that detract from the therapeutic efficacy of the drug. These problems arise from the tendency of the tablet when the patient is no longer in the fed mode to pass from the stomach into the small intestine, and over a period of 2–4 hours to pass through the small intestine, thus reaching the colon with the drug still in the tablet. This loss of effectiveness occurs with drugs that provide their maximum benefit with minimum side effects when absorbed in the stomach and upper GI tract rather than the colon. The reasons are either favorable conditions in the stomach, unfavorable conditions in the colon, or both.

For example, most orally administered antibiotics have a potential of altering the normal flora of the gastrointestinal tract, and particularly the flora of the colon. One result of these alterations is the overgrowth of the organism *Clostridium difficile,* which is a serious adverse event since this organism releases dangerous toxins. These toxins can cause pseudomembranous colitis, a condition that has been reported as a side effect of the use of many antibiotics. In its milder forms, pseudomembranous colitis can cause mild nausea and diarrhea while in its stronger forms, it can be life-threatening or fatal. Examples of highly soluble antibiotics that pose this type of threat are amoxicillin, cefuroxime axetil, and clindamycin. Cefuroxime axetil (i.e., the axetil ester of cefuroxime), for example, becomes active when hydrolyzed to free cefuroxime, but when this occurs prior to absorption, it can be detrimental to essential bacterial flora. Hydrolysis to the active form typically occurs in the tissues into which the ester has been absorbed, but if the ester reaches the lower intestine, enzymes in the lower intestine cause the hydrolysis to occur in the intestine itself, which not only renders the drug unabsorbable but also converts the drug to the active form where its activity alters the flora. Examples of sparingly soluble antibiotics that pose the same type of threat are clarithromycin, azithromycin, ceftazidine, ciprofloxacin, and cefaclor.

A goal of the present invention is to avoid this type of alteration of the lower intestinal flora by delivering antibiotics, regardless of their level of solubility, in a manner that confines their delivery to the stomach and upper small intestine. Slow, continuous delivery from a gastric retentive system assures that both drug delivery and drug absorption are confined to the upper GI tract. More efficient delivery of antibiotics will also avoid transient overdosing which is a major cause of overgrowth of *Clostridium difficile.*

Another example is the class of drugs that are susceptible to degradation by exposure to gastric fluid, either by enzymes or low solution pH. The swellable hydrophilic matrix of the present invention protects the yet undelivered drug during the 4 to 6 hour delivery period during which the drug is continuously released while the dosage form is retained in the stomach. One example of such a drug is topiramate, a drug that is used for the treatment of epilepsy. Topiramate is absorbed preferentially high in the GI tract and is hydrolyzed by the acidic environment of the stomach. The dosage form and delivery system of the present invention will confine the delivery of the drug to the stomach and duodenum. As the drug diffuses out of the swollen matrix, it is susceptible to the acidic environment, but the undelivered drug is protected from degradation by the polymer matrix.

Another example is the class of drugs that are known to have an absorption window high in the GI tract, but are incompletely absorbed or have a wide absorption range, intrapatient as well as interpatient. One example of such a drug is cyclosporine, a drug of low solubility that is used as an immunosuppressant to reduce organ rejection in transplant surgery. In addition to this problem, cyclosporine is in general only incompletely absorbed (on the average around 30%), and the degree of absorption is highly variable from one patient to the next (ranging from about 5% to about 89%). The variability can be attributed in part to differences among the various disease states existing in the patients to whom the drug is administered, and differences in the length of time between the transplant surgery and the administration of the drug. The variability can also however be attributed to the poor aqueous solubility of the drug and to variations in the gastric emptying, variations in the length of time required for intestinal transit between the stomach and the colon, variations in mesenteric and hepatic blood flow, variations in lymph flow, variations in intestinal secretion and fluid volume, variations in bile secretion and flow, and variations in epithelial cell turnover. All of these variations are addressed by the dosage form and delivery system of the present invention, which by confining drug delivery to the stomach reduces these differences and maximizes the absorption of the cyclosporine.

Another example is the class of drugs that are susceptible to degradation by intestinal enzymes. The degradation occurs before the drug can be absorbed through the intestinal wall, leaving only a fraction of the administered dose available for the intended therapeutic action.

An example of a highly soluble drug that is susceptible to degradation by intestinal enzymes is the pro-drug doxifluridine (5'-deoxy-5-fluouridine (dFUR)). The activity of doxifluridine depends on its activation to 5-fluorouracil by pyrimidine nucleoside phosphorylases. These enzymes are found in tumors as well as in normal tissues, with their highest activity being in the small intestine. The activity of these enzymes in tumor cells is more than twice that of normal tissues. When doxifluridine is administered orally, it can be converted to 5-fluorouracil in the intestine before it reaches the tumors. 5-Fluorouracil is much more toxic than doxifluridine and causes intestinal toxicity (nausea and diarrhea) and severe damage to the intestinal villi. A goal of the present invention is to confine the absorption of doxifluridine to the stomach and upper GI tract, thereby avoiding or reducing its conversion to 5-fluorouracil and the attendant toxicity risk. A similar result is sought for other drugs with similar susceptibilities, such as cyclosporine and digoxin.

Another class of drugs whose effectiveness suffers when the drugs are not fully absorbed high in the GI tract are those that are susceptible to inactivation by drug transporters that

reside in lower gastrointestinal tract enterocytes. The inactivation occurs before the drug penetrates the intestinal wall, here again leaving only a fraction of the administered dose available for the intended therapeutic action. One example of a drug transporter is the p-glycoprotein efflux system, in which a p-glycoprotein acts as an absorption barrier to certain drugs that are substrates for the p-glycoprotein. The barrier acts by attaching to these drugs and transporting them drug back into the lumen, e.g., the stomach, duodenum, jejunum/ileum or colon, from which they were absorbed, or preventing them from being absorbed at all. This restriction of the drug to the interior of the GI tract is effectively an inactivation of the drug if the drug must pass out of the GI tract into the bloodstream to be effective. The p-glycoprotein effiux system is useful in many respects, such as preventing toxic compounds from entering the brain. It interferes however in some cases with the efficacy of certain drugs that would otherwise be absorbed. The p-glycoprotein concentration is lowest in the stomach and increases in concentration down the GI tract to the colon where the p-glycoprotein is most prevalent. The dosage form of the present invention will release the drug over an extended period into the upper GI tract where p-glycoprotein is lowest.

Cyclosporine is an example of a drug of low solubility that is susceptible to inactivation by the p-glycoprotein effiux system, in addition to its susceptibility to degradation by colonic bacterial enzymes. Other examples of drugs of low solubility that are susceptible to the p-glycoprotein effiux system are the anti-cancer drug paclitaxel, ciprofloxacin, and the HIV protease inhibitors saquinavir, ritonavir, and nelfinavir. All of these drugs will benefit through preserved activity by the present invention.

A still further class of drugs that suffer in effectiveness when not fully absorbed before reaching the colon are drugs that require an acidic environment for effective bioavailability. For certain drugs, the pH at a given site within the GI tract is an essential determinant of the bioavailability of the drug, since the solubility of the drug varies with pH. The stomach has a low pH and hence an acidic environment, while the small intestine has a higher pH and hence an alkaline environment. Higher bioavailability is achieved in some cases by higher solubility, which with some drugs occurs in a more acidic environment, and in other cases by keeping the drugs in a non-ionized state that is necessary for absorption, which with some drugs also occurs in a more acidic environment. Acidic drugs that have a low pK, for example, are in the neutral form that is required for absorption and are therefore preferentially absorbed in the stomach. Examples of highly soluble drugs that achieve their highest bioavailability at a low pH are esters of ampicillin. Examples of low solubility drugs that behave similarly are iron salts, digoxin, ketoconazole, fluconazole, griseofulvin, itraconazole, and micoconazole. A further goal of the present invention is therefore to maximize the bioavailability of drugs of these types by confining them to the acidic environment of the stomach while controlling their release rate to achieve an extended release profile. The invention thus improves the efficiency of iron salts in the treatment of the various forms of anemia, the efficiency of digoxin in the treatment of the heart disease, and the efficiency of ketoconazole in the treatment of systemic fungal infections such as candidiasis, canduria, blastomycosis, coccidiomycosis, histoplasmosis, chronomycosis, and pacococcidiomycosis.

The invention also improves the efficiency of drugs that have at least one ionized group in the pH range of 5 through 8. Since this is the pH range encountered in the small

intestine and the region of the colonic junction and ionized drugs are less absorbable than neutral drugs, this invention improves the absorption of these drugs by retaining them in the stomach environment. The invention also improves the efficiency of drugs that are degradable in an acidic environment such as that of the stomach by protecting them from the acidic environment until they are released from the dosage form, thereby reducing the duration of their exposure to the acidic environment.

A still further example of drugs that lose their efficacy upon reaching the lower portions of the GI tract are drugs that are soluble in an acidic environment but insoluble in an alkaline environment. The HIV protease inhibitor nelfinavir mesylate is one example of such a drug. Portions of the drug that are undissolved cannot be absorbed. Portions that are dissolved but not yet absorbed when they pass from the stomach into the small intestine may undergo precipitation and loss of their therapeutic benefit. This is confirmed by the fact that the presence of food in the GI tract substantially increases the extent of absorption of oral nelfinavir. Peak plasma concentration and area under the plasma concentration-time curve of nelfinavir are two-fold to three-fold greater when doses are administered with or following a meal. This is presumably due, at least in part, to enhanced retention of the drug in the stomach. A further goal of the present invention is therefore to provide a means of administering these drugs that will maximize their therapeutic effectiveness by extended, controlled release into the stomach.

SUMMARY OF THE INVENTION

It has now been discovered that drugs that are highly soluble in water can be administered orally in a manner that will prolong their delivery time to spread their release rate more evenly throughout the duration of the fed mode and beyond or not as desired. This significantly reduces, and often avoids, the problems of transient overdosing caused by the initial spike in concentration entering the blood stream immediately after administration and the subsequent underdosing, and instead controls the dosage to safer and more effective levels over an extended period of time.

It has further been discovered that for drugs of high, intermediate or low solubility, the problems arising from the release of the drugs in the lower GI tract, i.e., from the failure to absorb these drugs into the blood stream prior to reaching the lower GI tract, can be mitigated as well. For all drugs regardless of solubility, therefore, this invention corrects problems such as the overgrowth of detrimental intestinal flora by drugs that are toxic to normal intestinal flora, protection of undelivered acid-labile drugs in the dosage form, chemical degradation of drugs by intestinal enzymes, loss of bioavailability of the drugs due to their leaving the acidic environment of the stomach, and chemical degradation of the drugs due to the alkaline environment of the intestinal tract. By mitigating these problems, this invention thus further improves the efficiency of the use of these drugs.

Each of the beneficial effects enumerated above is achieved by using a formulation in which the drug is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the drug primarily by diffusion. It has further been found that the rate of diffusion of the drug out of the matrix can be slowed by increasing the drug particle size, by the choice of polymer used in the matrix, and/or by the choice of molecular weight of the polymer. The matrix is a relatively high molecular weight polymer that swells upon ingestion, preferably to a size that is at least about twice its unswelled volume, and that promotes gastric retention during the fed mode. Upon swelling, the matrix may also convert over a prolonged period of time from a glassy polymer to a polymer that is rubbery in consistency, or from a crystalline polymer to a rubbery one. The penetrating fluid then causes release of the drug in a gradual and prolonged manner by the process of solution diffusion, i.e., dissolution of the drug in the penetrating fluid and diffusion of the dissolved drug back out of the matrix. The matrix itself is solid prior to administration and, once administered, remains undissolved in (i.e., is not eroded by) the gastric fluid for a period of time sufficient to permit the majority of the drug to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of the drug is therefore controlled diffusion of the drug from the matrix rather than erosion, dissolving or chemical decomposition of the matrix.

For highly soluble drugs, the swelling of the polymeric matrix thus achieves two objectives—(i) the tablet swells to a size large enough to cause it to be retained in the stomach during the fed mode, and (ii) it retards the rate of diffusion of the highly soluble drug long enough to provide multi-hour, controlled delivery of the drug into the stomach. For drugs that are either sparingly soluble, of limited solubility, or of high solubility, and that experience any of the specific problems enumerated above upon reaching the lower GI tract prior to absorption into the bloodstream, the swelling of the polymeric matrix (i) renders the matrix sufficiently large to cause retention in the stomach during the fed mode, and (ii) localizes the release of the drug to the stomach and small intestine so that the drug will have its full effect without colonic degradation, inactivation, or loss of bioavailability.

In either of these aspects, the invention provides an effective means of using these drugs to treat local stomach disorders as well as a wide variety of disease conditions. For example, use of this invention provides more effective eradication of ulcer-causing bacteria in the gastric mucosa with soluble antibiotics. The invention also provides enhanced absorption of soluble drugs that are absorbed mostly in the stomach or high in the gastrointestinal tract, such as metformin hydrochloride or ciprofloxacin. The invention is also useful in providing a multi-hour flow of a drug past the upper part of the small intestine (the most efficient absorption site for many agents).

Details of these and other features of the invention will be apparent from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plot showing the release rate of metformin hydrochloride from three different compositions of the drug in poly(ethylene oxide) matrices.

FIG. **2** is a plot showing the release rate of captopril from a poly(ethylene oxide) matrix, in accordance with this invention, both with and without glyceryl monostearate as a solubility modifier.

FIG. **3** is a plot showing the release rate of captopril from hydroxyethyl cellulose, in which the pellet size was varied.

FIG. **4** is a plot showing the release rate of metformin hydrochloride from various polymeric matrices.

FIG. **5** is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

FIG. **6** is a plot showing the release rate of captopril from various polymeric matrices.

FIG. **7** is a plot showing further release rate studies of metformin hydrochloride from two different polymeric matrices.

FIG. **8** is a plot showing the release rate of vancomycin hydrochloride from different polymeric matrices.

FIG. **9** is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

In aspects of this invention that are directed to highly soluble drugs, the drugs thus addressed are those that are characterized by the United States Pharmacopeia XXII as at least "freely soluble" in water, i.e., drugs whose solubility is greater than one part of the drug in about ten parts of water. Drugs of particular interest are those whose solubility is greater than one part in about five parts of water, and drugs of even greater interest are those whose solubility is greater than one part in about three parts of water. The parts referred to in this paragraph and throughout this specification are parts by weight.

The term "drug" is used herein to denote any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a therapeutic effect in the treatment of a disease or abnormal physiological condition. Examples of drugs of high solubility to which this invention is applicable are metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, doxifluridine, tramadol, fluoxitine hydrochloride, ciprofloxacin, gancyclovir, bupropion, lisinopril, and esters of ampicillin. Examples of drugs of low solubility to which this invention is applicable are cefaclor, ciprofloxacin, saguinavir, ritonavir, nelfinavir, clarithromycin, azithiomycin, ceftazidine, cyclosporin, digoxin, paclitaxel, iron salts, topiramate, and ketoconazole. Other drugs suitable for use and meeting the solubility criteria described above will be apparent to those skilled in the art. Drugs of particular interest are metformin hydrochloride and sertraline hydrochloride. The drug loadings (weight percent of drug relative to total of drug and polymer) in most of these cases will be about 80% or less.

The invention is also of use with drugs that have been formulated to include additives that impart a small degree of hydrophobic character, to further retard the release rate of the drug into the gastric fluid. One example of such a release rate retardant is glyceryl monostearate. Other examples are fatty acids and salts of fatty acids, one example of which is sodium myristate. The quantities of these additives when present can vary; and in most cases, the weight ratio of additive to drug will range from about 1:20 to about 1:1, and preferably from about 1:8 to about 1:2.

The water-swellable polymer forming the matrix in accordance with this invention is any polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of an incorporated drug. Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone), starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly (ethyleneimine), polyurethane hydrogels, and crosslinked polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers. Specific examples of copolymers are PLURONIC® and TECTONIC®, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA.

The terms "cellulose" and "cellulosic" are used herein to denote a linear polymer of anhydroglucose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C. Particularly preferred alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

Polyalkylene oxides of greatest utility in this invention are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Poly(ethylene oxide) polymers having molecular weights of about 4,000,000 and higher are preferred. More preferred are those with molecular weights within the range of about 4,500,000 to about 10,000,000, and even more preferred are polymers with molecular weights within the range of about 5,000,000 to about 8,000,000. Preferred poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about 1×10^5 to about 1×10^7, and preferably within the range of about 9×10^5 to about 8×10^6. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For purposes of this invention, a preferred viscosity range is about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20° C. Two presently preferred poly(ethylene oxide)s are POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamsan gum. Xanthan gum is preferred.

Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Preferred crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25° C. Three presently preferred examples are CARBOPOL® NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples are polymers known as WATER LOCK®, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

The hydrophilicity and water swellability of these polymers cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the drug particle size and the drug concentration in the matrix. Also, because these polymers dissolve very slowly in gastric fluid, the matrix maintains its physical integrity over at least a substantial period of time, in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. Complete dissolution or decomposition may not occur until 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within 10 to 24 hours after the dosing period.

The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 40% of the drug within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 50% of the drug remains in the matrix one hour after ingestion. More preferably, at least 60%, and most preferably at least 80%, of the drug remains in the matrix one hour after ingestion. In all cases, however, the drug will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

The benefits of this invention will be achieved over a wide range of drug loadings, with the weight ratio of drug to polymer ranging in general from 0.01:99.99 to about 80:20. Preferred loadings (expressed in terms of the weight percent of drug relative to total of drug and polymer) are those within the range of 15% to 80%, more preferably within the range of 30% to 80%, and most preferably in certain cases within the range of about 30% to 70%. For certain applications, however, the benefits will be obtained with drug loadings within the range of 0.01% to 80%, and preferably 15% to 80%.

The formulations of this invention may assume the form of particles, tablets, or particles retained in capsules. A preferred formulation consists of particles consolidated into a packed mass for ingestion, even though the packed mass will separate into individual particles after ingestion. Conventional methods can be used for consolidating the particles in this manner. For example, the particles can be placed in gelatin capsules known in the art as "hard-filled" capsules and "soft-elastic" capsules. The compositions of these capsules and procedures for filling them are known among those skilled in drug formulations and manufacture. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested.

In certain embodiments of this invention, the formulation contains an additional amount of the drug applied as a quickly dissolving coating on the outside of the particle or tablet. This coating is referred to as a "loading dose" and it is included for immediate release into the recipient's bloodstream upon ingestion of the formulation without first undergoing the diffusion process that the remainder of the drug in the formulation must pass before it is released. The "loading dose" is high enough to quickly raise the blood concentration of the drug but not high enough to produce the transient overdosing that is characteristic of highly soluble drugs that are not formulated in accordance with this invention.

One presently preferred dosage form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, 6.6 or 6.7 mm (or more generally, 6.5 to 7 mm) in diameter and 9.5 or 10.25 mm (or more generally, 9 to 12 mm) in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6.6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.25 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 7.5 mm in length. Another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 10 mm in width, and 5 to 7.5 mm in height. Still another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 7.8 mm in width, and 6.2 to 7.5 mm in height. A preferred set of dimensions is 20 mm in length, 6.7 mm in width, and 6.4 mm in height. These are merely examples; the shapes and sizes can be varied considerably.

The particulate drug/polymer mixture or drug-impregnated polymer matrix can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such techniques are as follows:

(1) Direct compression, using appropriate punches and dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pa., USA; the punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pa., USA;

(2) Injection or compression molding using suitable molds fitted to a compression unit, such as those available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.;

(3) Granulation followed by compression; and

(4) Extrusion in the form of a paste, into a mold or to an extrudate to be cut into lengths.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the particle) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight,

preferably less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular drug, including both its pharmacological characteristics and its physical characteristics such as solubility, and with the characteristics of the swellable matrix such as its permeability, and the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight hours or more, preferably once every twelve hours or more, and even more preferably once every twenty-four hours or more.

As indicated above, the dosage forms of the present invention find their greatest utility when administered to a subject who is in the digestive state (also referred to as the postprandial or "fed" mode). The postprandial mode is distinguishable from the interdigestive (or "fasting") mode by their distinct patterns of gastroduodenal motor activity, which determine the gastric retention or gastric transit time of the stomach contents.

In the interdigestive mode, the fasted stomach exhibits a cyclic activity called the interdigestive migrating motor complex (IMMC). The cyclic activity occurs in four phases:

- Phase I is the most quiescent, lasts 45 to 60 minutes, and develops few or no contractions.
- Phase II is marked by the incidence of irregular intermittent sweeping contractions that gradually increase in magnitude.
- Phase III, which lasts 5 to 15 minutes, is marked by the appearance of intense bursts of peristaltic waves involving both the stomach and the small bowel.
- Phase IV is a transition period of decreasing activity which lasts until the next cycle begins.

The total cycle time is approximately 90 minutes, and thus, powerful peristaltic waves sweep out the contents of the stomach every 90 minutes during the interdigestive mode. The IMMC may function as an intestinal housekeeper, sweeping swallowed saliva, gastric secretions, and debris to the small intestine and colon, preparing the upper tract for the next meal while preventing bacterial overgrowth. Pancreatic exocrine secretion of pancreatic peptide and motilin also cycle in synchrony with these motor patterns.

The postprandial or fed mode is induced by food ingestion, and begins with a rapid and profound change in the motor pattern of the upper GI tract, the change occurring over a period of 30 seconds to one minute. The stomach generates 3–4 continuous and regular contractions per minute, similar to those of the interdigestive mode but of about half the amplitude. The change occurs almost simultaneously at all sites of the GI tract, before the stomach contents have reached the distal small intestine. Liquids and small particles flow continuously from the stomach into the intestine. Contractions of the stomach result in a sieving process that allows liquids and small particles to pass through a partially open pylorus. Indigestible particles greater than the size of the pylorus are retropelled and retained in the stomach. Particles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours. The dosage form of the present invention is designed to achieve the minimal size through swelling following ingestion during the fed mode.

The following examples are offered for purposes of illustration, and are not intended to limit the invention in any manner.

EXAMPLE 1

This example illustrates the controlled-release behavior of metformin hydrochloride, a highly soluble drug (whose solubility is approximately 30%), from a polymeric matrix consisting of poly(ethylene oxide). Three different dose levels were prepared—systems designed to release 90% of their drug contents at approximately 3 hours, 6 hours, and 8 hours, respectively.

Drug and polymer, with 0.5% magnesium stearate as a tableting lubricant, were compressed into pellets measuring 7.2 mm diameter×8.8 mm length and weighing 390 mg for samples designed for 3-hour and 6-hour release, and 7.4 mm diameter×8.5 mm length and weighing 380 mg for samples designed for 8-hour release, and two pellets of a given type were incorporated into a single gelatin capsule. Thus, three different types of gelatin capsule were prepared as follows:

$t_{90\%} \cong$ 3 hours:	
metformin hydrochloride	250.00 mg
POLYOX ® 1105, molecular weight 900,000	138.67
magnesium stearate	1.95
Total:	390.62 mg
$t_{90\%} \cong$ 6 hours:	
metformin hydrochloride	250.00 mg
POLYOX ® Coagulant, molecular weight 5,000,000	138.67
magnesium stearate	1.95
Total:	390.62 mg
$t_{90\%} \cong$ 8 hours:	
metformin hydrochloride	125.00 mg
POLYOX ® 303, molecular weight 7,000,000	266.11
magnesium stearate	1.97
Total:	393.08 mg

Release rate tests on each of these three formulations were performed in modified artificial gastric fluid by the following procedure.

Dissolution was performed in a USP Apparatus 2, modified to include a stainless steel cone (⅞ inch in height and ⅞ inch in diameter at the base) at the bottom of each vessel, placed directly beneath the paddle shaft to eliminate the "dead zone" effect. A paddle speed of 60 rpm and a bath temperature of 37.4° C. were used. The gelatin capsule was opened and the individual pellets and empty gelatin capsule were dropped into the dissolution vessel containing 900 mL of modified simulated gastric fluid (7 mL of hydrochloric acid and 2 g of sodium chloride in 100 mL of deionized water; the enzyme pepsin was omitted). Once the pellets had settled to the bottom of the vessel, the paddle rotation was initiated. Samples 5 mL in size were taken at specified time points, and the sample volumes were not replaced. The samples were diluted as necessary for quantitative analysis by HPLC.

The results are shown in FIG. **1**, where the filled diamonds represent the $t_{90\ \%}\cong 3$ formulation, the x's represent the $t_{90\ \%}\cong 6$ formulation, and the open circles represent the $t_{90\ \%}\cong 8$ formulation. The curves show that the $t_{90\ \%}$ value of the first formulation was fairly close to 3.5 hours, the $t_{90\ \%}$ value of the second formulation was fairly close to 6.0 hours, and $t_{90\%}$ value of the third formulation was fairly close to 7.5 hours.

EXAMPLE 2

This example illustrates the controlled-release behavior of captopril from a polymeric matrix consisting of poly (ethylene oxide), both with and without glyceryl monostearate (8% by weight). The formulations used were as follows:

1.	Captopril	92.50 mg
	Poly(ethylene oxide)(POLYOX ® 301), molecular weight 4,000,000	407.50
	Total	500.00 mg
2.	Captopril	92.5 mg
	glyceryl monostearate	15.0
	Poly(ethylene oxide)(POLYOX ® 301), molecular weight 4,000,000	392.5
	Total	500.0 mg

Each formulation was compressed into a tablet measuring 6.0 mm diameter×6.7 mm length and weighing 180 mg. Release rate tests on each of the two tablets were performed in modified simulated gastric fluid by the procedure of Example 1, except that the paddle rotation speed was 30 rpm and the tablets were dropped directly into the dissolution vessel.

The results are shown in FIG. **2**, where the filled squares represent Formulation No. 1 consisting of captopril and poly(ethylene oxide) only, and the open circles represent Formulation No. 2 which further contained glyceryl monostearate.

EXAMPLE 3

This example illustrates the controlled-release behavior of captopril from a polymeric matrix of hydroxyethyl cellulose with the inclusion of glyceryl monostearate, but at varying pellet sizes. The formulation contained 19% captopril (all percents by weight) and 4.8% glyceryl monostearate in hydroxyethyl cellulose of molecular weight within the range of 1,000,000 to 1,500,000. The pellet sizes and weights were (a) 3.3 mm diameter×3.5 mm length at 35 mg (referred to herein as 3-mm tablets), (b) 4.3 mm diameter×4.9 mm length at 75 mg (referred to herein as 4-mm tablets), and (c) 6.3 mm diameter×6.5 mm length at 187 mg (referred to herein as 6-mm tablets).

Release rate tests on each of the three tablet sizes (fifteen of the 3-mm tablets, seven of the 4-mm tablets, and three of the 6-mm tablets) were performed using the procedures of Example 1, except that a weighted watchglass was used in place of the stainless steel cone, and analyses of the samples were performed by UV/Vis. The results are shown in FIG. **3**, where the filled squares represent the 3-mm pellets, the filled triangles the 4-mm pellets, and the filled circles the 6-mm pellets. This demonstrates the variation of pellet size as a further means of varying the release pattern, the larger pellets having less surface area.

EXAMPLE 4

This example further illustrates the controlled release of metformin hydrochloride, using a higher drug loading, and various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **4** where the results are plotted, were as follows (all percentages are by weight):

Filled circles: 79.6% metformin HCl; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.04 mm diameter×9.48 mm length; containing approximately 478 mg metformin HCl.

Filled squares: 79.6% metformin HCl; 20% xanthan gum (KELTROL® F, Kelco, Div. of Merck & Co., Inc., San Diego, Calif., USA); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.40 mm length; containing approximately 483 mg metformin HCl.

Plus signs: 79.6% metformin HCl; 20% hydroxypropylmethyl cellulose (BENECEL® 824, Aqualon Co., Wilmington, Del., USA), viscosity (2%, 20° C.) 11,000 to 15,000 cps; 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.49 mm length; containing approximately 480 mg metformin HCl.

Open diamonds: 79.6% metformin HCl; 5% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 15% poly(ethylene oxide (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.60 mm length; containing approximately 480 mg metformin HCl.

x's: 79.6% metformin HCl, 18.05% xanthan gum (KELTROL®F); 1.99% WATER LOCK® D-223 (starch graft poly(2-propenamide-co-2-propenoic acid)), mixed sodium and aluminum salts, Grain Processing Corporation, Muscatine, Iowa, USA); 0.4% magnesium stearate. Pellet dimensions were 6.06 mm diameter×9.24 mm length; containing approximately 476 mg metformin HCl total.

EXAMPLE 5

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **5**. The formulation was as follows (all percentages are by weight): 64% metformin HCl; 35.5% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 6.48 mm diameter×7.20 mm height×19.21 mm length, and contained approximately 506 mg metformin HCl per tablet.

EXAMPLE 6

This example further illustrates the controlled release of captopril, using various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **6** where the results are plotted, were as follows (all percentages are by weight):

Plus signs: 80% captopril; 20% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.03 mm diameter×9.25 mm length, 2 pellets weighing 293 mg each, containing approximately 469 mg captopril total.

Filled diamonds: 80% captopril; 20% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter× 9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Filled triangles: 80% captopril; 20% hydroxyethyl cellulose (250HX, molecular weight 1,000,000). Pellet dimensions: 6.03 mm diameter×9.53 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open circles: 80% captopril; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.59 mm length, 2 pellets weighing 301 mg each, containing approximately 482 mg captopril total.

Filled squares: 80% captopril; 20% carboxymethyl cellulose (12M31P, molecular weight 250,000). Pellet dimensions: 6.04 mm diameter×9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open triangles: 79.93% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.04% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter×9.26 mm length, 2 pellets weighing 296 mg each, containing approximately 473 mg captopril total.

x's: 79.96% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.01% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

Dashes: 80% captopril; 10% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 298 mg each, containing approximately 477 mg captopril total.

Open diamonds: 79.96% captopril; 18.05% xanthan gum (KELTROL® F); 1.99% WATERLOCK® D-223. Pellet dimensions: 6.04 mm diameter® 9.16 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

EXAMPLE 7

This example presents further data on metformin hydrochloride formulations, illustrating the effect of lower drug loadings than those used in the preceding examples. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **7** where the results are plotted, were as follows (all percentages are by weight):

Filled squares: 32.5% metformin HCl; 67% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions 6.62 mm diameter×10.40 mm length, 2 pellets weighing 400 mg each, containing approximately 260 mg metformin HCl total.

Open circles: 32.5% metformin HCl; 67% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions 6.65 mm diameter×9.28 mm length; 2 pellets weighing 401 mg each, containing approximately 261 mg metformin HCl total.

EXAMPLE 8

This example illustrates the sustained release of vancomycin hydrochloride from various polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **8** where the results are plotted, were as follows (all percentages are by weight):

Open squares: 31.5% vancomycin hydrochloride; 68% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.23 mm length, 2 pellets weighing 403 mg each, containing approximately 254 mg vancomycin hydrochloride total.

Open triangles: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX® 301, molecular weight 4,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.28 mm length, 2 pellets weighing 402 mg each, containing approximately 253 mg vancomycin hydrochloride total.

x's: 31.5% vancomycin hydrochloride; 68% hydroxypropyl methylcellulose (BENECEL® 824, viscosity 11,000–15,000 cps (2% solution at 20° C.)); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.10 mm length, 2 pellets weighing 405 mg each, containing approximately 255 mg vancomycin hydrochloride total.

Open circles: 31.5% vancomycin hydrochloride; 68% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions: 6.62 mm diameter×9.77 mm length, 2 pellets weighing 401 mg each, containing approximately 253 mg vancomycin hydrochloride total.

Filled squares: 62.5% vancomycin hydrochloride; 37% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.60 mm diameter×10.01 mm length, 2 pellets weighing 409 mg each, containing approximately 511 mg vancomycin hydrochloride total.

In the prior art, vancomycin and its salts are administered by injection, due to poor absorption when administered orally. By providing for all or at least a portion of the total administered amount to be delivered by controlled delivery in the gastric retentive system of this invention, that portion so delivered is directed to the proximal portion of the small intestine, the most efficient site for absorption of this drug, resulting in an enhanced absorption from the oral dosage form of the invention.

EXAMPLE 9

This example illustrates the difference between subjects in the fed mode and subjects not in the fed mode in terms of the gastric retention of tablets of various sizes administered orally. Both Beagle dogs and human subjects were used.

Barium-containing tablets for oral administration were prepared from the following ingredients:

25%	Barium Sulfate
30%	PolyOx 303 (average molecular weight 7,000,000)
44.5%	Hydroxypropylcellulose
0.5%	Magnesium Stearate

For tests on Beagle dogs, 400-mg tablets measuring 5.8 mm diameter×5.1 mm height×15.4 mm length were prepared in a tablet press at 2,500 psi pressure, and 800-mg tablets measuring 7.9 mm diameter×5.6 mm height×19.1 mm length were prepared in a tablet press at 5,000 psi. Four beagle dogs were used, and the location of the tablets in the GI tract was followed using fluoroscopy. Two studies were initiated with the dogs. In the first study, each dog received two tablets (one 400-mg and one 800-mg) with a small amount of water after a 16-hour fast. In the second study, each dog received two tablets (one 400-mg and one 800-mg) thirty minutes after ingesting 50 grams of a standard meal. The location of the tablets (in or out of the stomach) was monitored every 30 minutes with the fluoroscope.

The fluoroscopy revealed that tablets that were administered while the dogs were in the fasted condition were

emptied from the dogs' stomachs within 90 minutes: in two of the dogs, the stomachs contained no barium tablets at 30 minutes, in a third this was true at 60 minutes, and in the fourth at 90 minutes. Tablets that were administered while the dogs were in the fed state remained in the dogs' stomach for between 4 and 5 hours.

Human tests were performed on ten normal adults of both sexes, each taking part in two trials, the first after fasting and the second after a bacon and egg breakfast of approximately 1,500 calories. The tablets used in the tests had the same composition as those used for the Beagle dogs and measured either 4 mm×4 mm or 6 mm×6 mm. The subjects were X-rayed at 30 minutes and at 1, 2, 4, 6, 8, 10, and approximately 12 hours after ingesting the tablets. In some subjects, visualization was achieved by ultrasound rather than X-rays.

Imaging revealed that in the fasted trials, the tablets left the stomach in 30 minutes to one hour after administration. In the fed trials, the tablets demonstrated multiple-hour retention in the stomach in all subjects, 80% of the contents of all tablets being retained at 4 hours. Five of the ten subjects retained the tablets for 6 hours or more, and four of these five retained them for ten hours or more.

EXAMPLE 10

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **9**. The formulation was as follows (all percentages are by weight): 48.5% metformin HCl; 49% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 9.66 mm diameter×6.95 mm height×19.24 mm length, and contained approximately 506 mg metformin HCl per tablet.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, additives, proportions, methods of formulation, and other parameters of the invention can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed is:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20, said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug after such immersion, and that remains substantially intact until substantially all of said drug is released.

2. A dosage form in accordance with claim **1** in which the solubility of said drug in water is greater than one part by weight of said drug in five parts by weight of water.

3. A dosage form in accordance with claim **1** in which said drug is a member selected from the group consisting of metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, tramadol and ticlopidine hydrochloride.

4. A dosage form in accordance with claim **1** in which said drug is metformin hydrochloride.

5. A dosage form in accordance with claim **1** in which said drug is sertraline hydrochloride.

6. A dosage form in accordance with claim **1** in which said drug is captopril.

7. A dosage form in accordance with claim **1** in which said drug is vancomycin hydrochloride.

8. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

9. A dosage form in accordance with claim **8** in which said alkyl-substituted celluloses are members selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

10. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

11. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 4,500,000 to about 10,000,000.

12. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 5,000,000 to about 8,000,000.

13. A dosage form in accordance with claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said drug one hour after such immersion.

14. A dosage form in accordance with claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said drug one hour after such immersion.

15. A dosage form in accordance with claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 80% of said drug one hour after such immersion.

16. A dosage form in accordance with claim **1** further comprising a member selected from the group consisting of glyceryl monostearate and sodium myristate, formulated with said drug to further retard the release of said drug to said gastric fluid.

17. A dosage form in accordance with claim **1** in which said polymeric matrix consists of two cylindrical tablets, each measuring about 9 mm to about 12 mm in length and about 6.5 mm to about 7 mm in diameter.

18. A dosage form in accordance with claim **1** in which said polymeric matrix consists of a single elongated tablet measuring about 18 mm to about 22 mm in length, about 6.5 mm to about 7.8 mm in width, and about 6.2 to 7.5 mm in height.

19. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also capable of altering intestinal flora in a manner detrimental to the health of said subject, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

20. A method in accordance with claim **19** in which said drug is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, ceftazidine, and ciprofloxacin.

21. A method in accordance with claim **19** in which said drug is a highly soluble drug selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, and clindamycin.

22. A method of treating a subject suffering from infections selected from the group consisting of pneumonia, sinus bacterial infections, topical bacterial infections and staphylococcus infections, by administering to said subject a drug which is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, and ceftazidine, without substantially causing side effects resulting from the alteration of the intestinal flora of said subject, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

23. A method in accordance with claim **22** in which said drug is a highly soluble drug selected from the group consisting of amoxiillin, cefuroxime axetil, cefaclor, and clindamycin.

24. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable by colonic bacterial enzymes residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal enzymes and said drug transporters.

25. A method in accordance with claim **24** in which said drug is a member selected from the group consisting of cyclosporine, digoxin, and doxifluridine.

26. A method in accordance with claim **24** in which said drug is doxifluridine.

27. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial degradation of said cyclosporine by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said cyclosporine incorporated therein at a weight ratio of cyclosporine to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid, and

(d) releases substantially all of said cyclosporine within about ten hours after such immersion,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding contact of said cyclosporine with said colonic bacterial enzymes.

28. A method of treating a subject for heart disease by administering digoxin to said subject without substantial degradation of said digoxin by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said digoxin while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said digoxin incorporated therein at a weight ratio of digoxin to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said digoxin one hour after such immersion in gastric fluid, and

(d) releases substantially all of said digoxin within about ten hours after such immersion,

thereby extending the release rate of said digoxin with time during said fed mode while releasing substantially all of said digoxin within said stomach and substantially avoiding contact of said digoxin with said colonic bacterial enzymes.

29. A method of treating a subject suffering from a condition selected from the group consisting of ovarian cancer, colorectal cancer, gastric cancer, renal cancer, and breast cancer, by administering doxifluridine to said subject without substantial degradation of said doxifluridine by intestinal enzymes or substantial inactivation of said doxifluridine by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said doxifluridine while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said doxifluridine incorporated therein at a weight ratio of doxifluridine to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said doxifluridine one hour after such immersion in gastric fluid, and

(d) releases substantially all of said doxifluridine within about ten hours after such immersion,

thereby extending the release rate of said doxifluridine with time during said fed mode while releasing substantially all of said doxifluridine within said stomach and substantially avoiding contact of said doxifluridine with said enzymes.

30. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also susceptible to inactivation by drug transporters residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form one or more polymers forming comprising a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said drug transporters.

31. A method in accordance with claim **30** in which said drug is a member selected from the group consisting of cyclosporine and paclitaxel.

32. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial inactivation of said cyclosporine by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said cyclosporine incorporated therein at a weight ratio of cyclosporine to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid, and

(d) releases substantially all of said cyclosporine within about ten hours after such immersion,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding inactivation of said cyclosporine by p-glycoprotein in said lower gastrointestinal tract.

33. A method of treating a subject suffering from cancer by administering paclitaxel to said subject without substantial inactivation of said paclitaxel by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said paclitaxel while said subject is in a fed mode, said dosage form comprising a one or more polymers forming solid polymeric matrix with said paclitaxel incorporated therein at a weight ratio of paclitaxel to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said paclitaxel one hour after such immersion in gastric fluid, and

(d) releases substantially all of said paclitaxel within about ten hours after such immersion,

thereby extending the release rate of said paclitaxel with time during said fed mode while releasing substantially all of said paclitaxel within said stomach and substantially avoiding inactivation of said paclitaxel by p-glycoprotein in said lower gastrointestinal tract.

34. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach

and whose bioavailability is substantially greater in an acidic environment than an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

35. A method in accordance with claim **34** in which said drug is a member selected from the group consisting of esters of ampicillin, iron salts, digoxin, and ketoconazole.

36. A method in accordance with claim **34** in which said drug is a member selected from the group consisting of esters of ampicillin.

37. A method of treating a subject suffering from a bacterial infection by administering an ester of ampicillin to said subject while maintaining maximum bioavailability of said ester of ampicillin, said method comprising orally administering to said subject a dosage form of said ester of ampicillin while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said ester of ampicillin incorporated therein at a weight ratio of said ester of ampicillin to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ester of ampicillin one hour after such immersion in gastric fluid, and

(d) releases substantially all of said ester of ampicillin within about ten hours after such immersion,

thereby extending the release rate of said ester of ampicillin with time during said fed mode while releasing substantially all of said ester of ampicillin within said stomach and maintaining said ester of ampicillin in the acidic environment of said stomach during said release.

38. A method of treating a subject suffering from anemia by administering iron salts to said subject while maintaining maximum bioavailability of said iron salts, said method comprising orally administering to said subject a dosage form of said iron salts while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said iron salts incorporated therein at a weight ratio of iron salts to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said iron salts one hour after such immersion in gastric fluid, and

(d) releases substantially all of said iron salts within about ten hours after such immersion,

thereby extending the release rate of said iron salts with time during said fed mode while releasing substantially all of said iron salts within said stomach where said iron salts are maintained in an acidic environment.

39. A method of treating a subject suffering from a systemic fungal infection by administering ketoconazole to said subject while maintaining maximum bioavailability of said ketoconazole, said method comprising orally administering to said subject a dosage form of said ketoconazole while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said ketoconazole incorporated therein at a weight ratio of ketoconazole to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ketoconazole one hour after such immersion in gastric fluid, and

(d) releases substantially all of said ketoconazole within about ten hours after such immersion,

thereby extending the release rate of said ketoconazole with time during said fed mode while releasing substantially all of said ketoconazole within said stomach where said ketoconazole is maintained in an acidic environment.

40. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix in which said drug is incorporated at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

41. A method in accordance with claim **40** in which said drug is nelfinar mesylate.

42. A method of treating a subject infected with human immunodeficiency virus by administering nelfinar mesylate to said subject without substantial degradation of said nelfinar mesylate by intestinal flora or substantial inactivation of said nelfinar mesylate by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said nelfinar mesylate while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said nelfinar mesylate incorporated therein at a weight ratio of nelfinar mesylate to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said nelfinar mesylate into gastric fluid by the dissolving of said nelfinar mesylate by said gastric fluid and either erosion of said matrix or diffusion of said dissolved nelfinar mesylate out of said matrix,

(c) retains at least about 40% of said nelfinar mesylate one hour after such immersion in gastric fluid, and

(d) releases substantially all of said nelfinar mesylate within about ten hours after such immersion,

thereby extending the release rate of said nelfinar mesylate with time during said fed mode while releasing substantially all of said nelfinar mesylate within said stomach where said nelfinar mesylate is maintained in an acidic environment.

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

44. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an acidic environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) protects any unreleased drug in said matrix from said gastric fluid,

(d) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(e) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

45. A dosage form in accordance with claim **1** in which said dosage form releases substantially all of said drug within about ten hours after immersion in gastric fluid.

46. A dosage form in accordance with claim **1** in which said dosage form releases substantially all of said drug within about eight hours after immersion in gastric fluid.

47. A dosage form in accordance with claim **4** in which said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

48. A dosage form in accordance with claim **4** in which said polymeric matrix comprises an alkyl-substituted cellulose.

49. A dosage form in accordance with claim **4** in which said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

50. A dosage form in accordance with claim **4** in which said polymeric matrix comprises hydroxypropylmethyl-cellulose.

51. A dosage form in accordance with claim **4** in which said polymeric matrix comprises hydroxypropylmethyl-cellulose having a viscosity ranging from 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

52. A dosage form in accordance with claim **4** in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said metformin hydrochloride one hour after such immersion.

53. A dosage form in accordance with claim **4** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

54. A dosage form in accordance with claim **4** in which said polymeric matrix comprises poly(ethylene oxide) having a molecular weight of at least about 4,000,000.

55. A dosage form in accordance with claim **4** in which said polymeric matrix comprises poly(ethylene oxide) having a molecular weight ranging from about 4,500,000 to about 10,000,000.

56. A dosage form in accordance with claim **4** in which said polymeric matrix comprises poly(ethylene oxide) hav-

ing a molecular weight ranging from about 5,000,000 to about 8,000,000.

57. A dosage form in accordance with claim **1** in which said drug is ciprofloxacin.

58. A dosage form in accordance with claim **57** in which said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

59. A dosage form in accordance with claim **57** in which said polymeric matrix comprises an alkyl-substituted cellulose.

60. A dosage form in accordance with claim **57** in which said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

61. A dosage form in accordance with claim **57** in which said polymeric matrix comprises hydroxypropylmethyl-cellulose.

62. A dosage form in accordance with claim **57** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

63. A dosage form in accordance with claim **57** in which said polymeric matrix comprises poly(ethylene oxide).

64. A dosage form in accordance with claim **1** in which said drug is an iron salt.

65. A dosage form in accordance with claim **64** in which said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

66. A dosage form in accordance with claim **64** in which said polymeric matrix comprises an alkyl-substituted cellulose.

67. A dosage form in accordance with claim **64** in which said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

68. A dosage form in accordance with claim **64** in which said polymeric matrix comprises hydroxypropylmethyl-cellulose.

69. A dosage form in accordance with claim **64** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

70. A dosage form in accordance with claim **64** in which said polymeric matrix comprises poly(ethylene oxide).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,635,280 B2
DATED : October 21, 2003
INVENTOR(S) : John W. Shell et al.

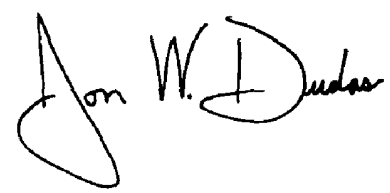
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27,
Line 24, delete "metformin hydrochloride", and insert -- ciprofloxacin --

Column 28,
Line 22, delete "metformin hydrochloride", and insert -- iron salts --

Signed and Sealed this

Twenty-second Day of June, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

US006340475B2

(12) **United States Patent**
Shell et al.

(10) **Patent No.: US 6,340,475 B2**
(45) **Date of Patent: *Jan. 22, 2002**

(54) **EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE**

(75) Inventors: **John W. Shell**, Hillsborough; **Jenny Louie-Helm**, Union City; **Micheline Markey**, Santa Cruz, all of CA (US)

(73) Assignee: **DepoMed, Inc.**, Menlo Park, CA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/282,233**

(22) Filed: **Mar. 29, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/870,509, filed on Jun. 6, 1997, now abandoned.

(51) **Int. Cl.**[7] **A61K 9/26**; A61K 9/14

(52) **U.S. Cl.** **424/469**; 424/464; 424/468; 424/488; 424/486; 424/487

(58) **Field of Search** 424/451, 457, 424/458, 464, 468, 469, 484, 485, 486, 489, 501, 502, 426

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WO	96/32097	10/1996
WO	98/11879	3/1998
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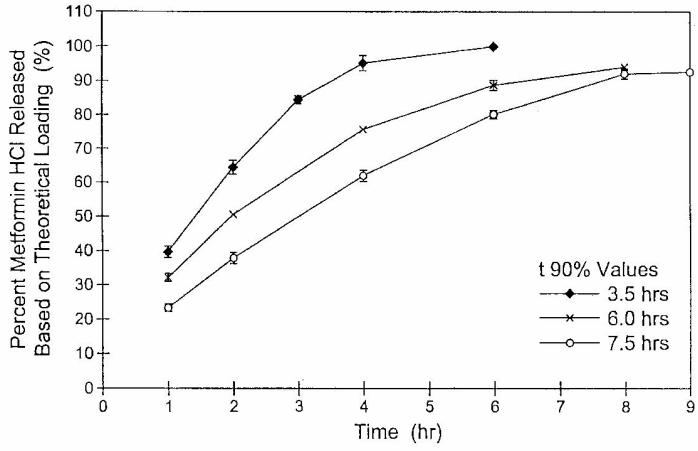
Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

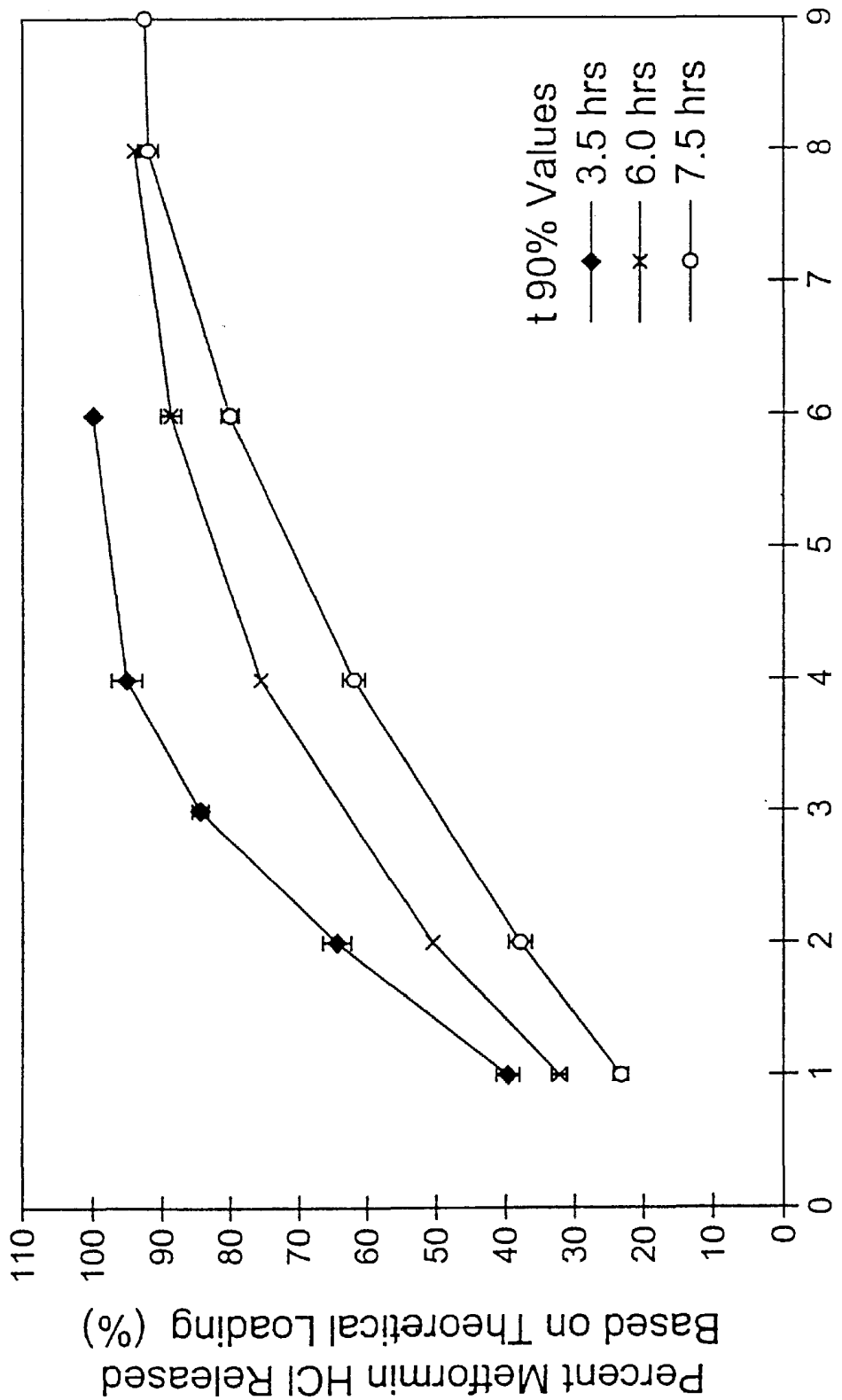
(57) **ABSTRACT**

Drugs are formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic polymers that swell upon imbibition of water to a size that is large enough to promote retention of the dosage form in the stomach during the fed mode. The oral formulation is designed for gastric retention and controlled delivery of an incorporated drug into the gastric cavity, and thus administered, the drug is released from the matrix into the gastric fluid by solution diffusion. The swollen polymeric matrix, having achieved sufficient size, remains in the gastric cavity for several hours if administered while the patient is in the fed mode, and remains intact long enough for substantially all of the drug to be released before substantial dissolution of the matrix occurs. The swelling matrix lowers the accessibility of the gastric fluid to the drug and thereby reduces the drug release rate. This process, together with diffusion retardation by selection of specific polymers, polymer molecular weights, and other variables, results in a sustained and controlled delivery rate of the drug to the gastric cavity.

89 Claims, 9 Drawing Sheets



Purdue Exhibit 1001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Based on Theoretical Loading (%)
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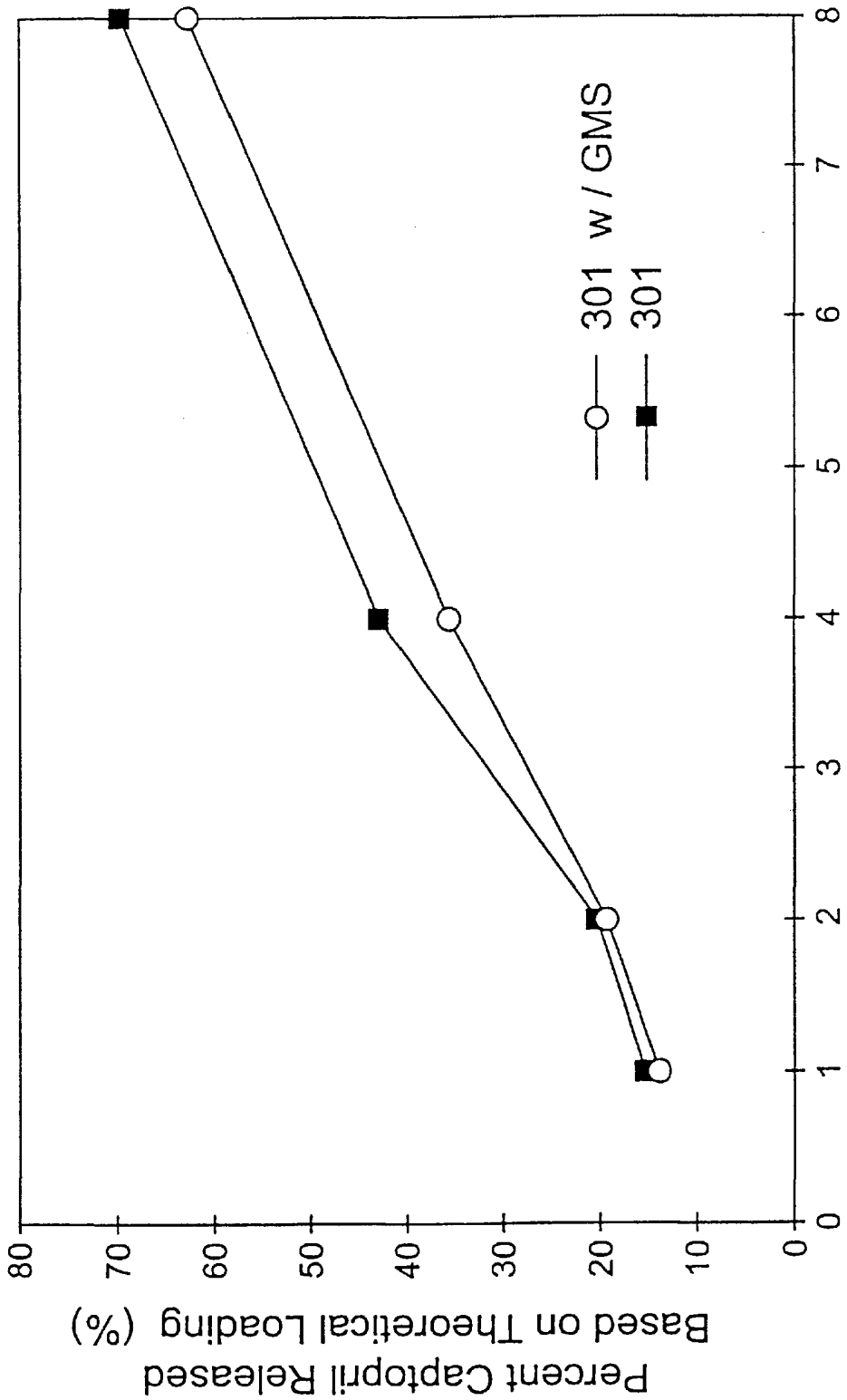
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (hr)
t 90% Values
3.5 hrs
6.0 hrs
7.5 hrs

Fig. 1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Based on Theoretical Loading (%)
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70
60
50
40
30
20
10
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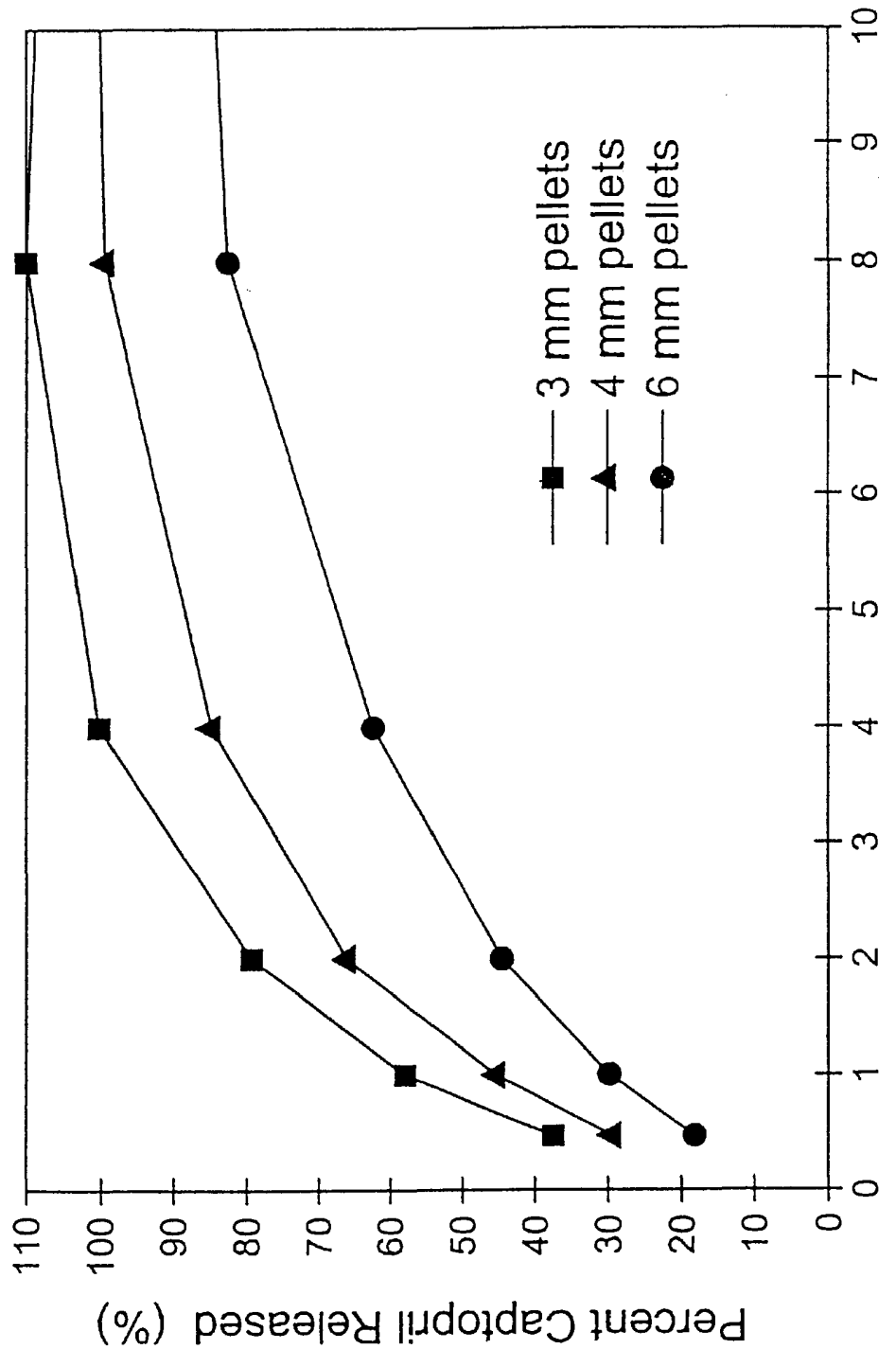
0
1
2
3
4
5
6
7
8
Time (hr)
301 w / GMS
301

Fig. 2


Percent Captopril Released (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
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5
6
7
8
9
10
Time (hr)
3 mm pellets
4 mm pellets
6 mm pellets

Fig. 3

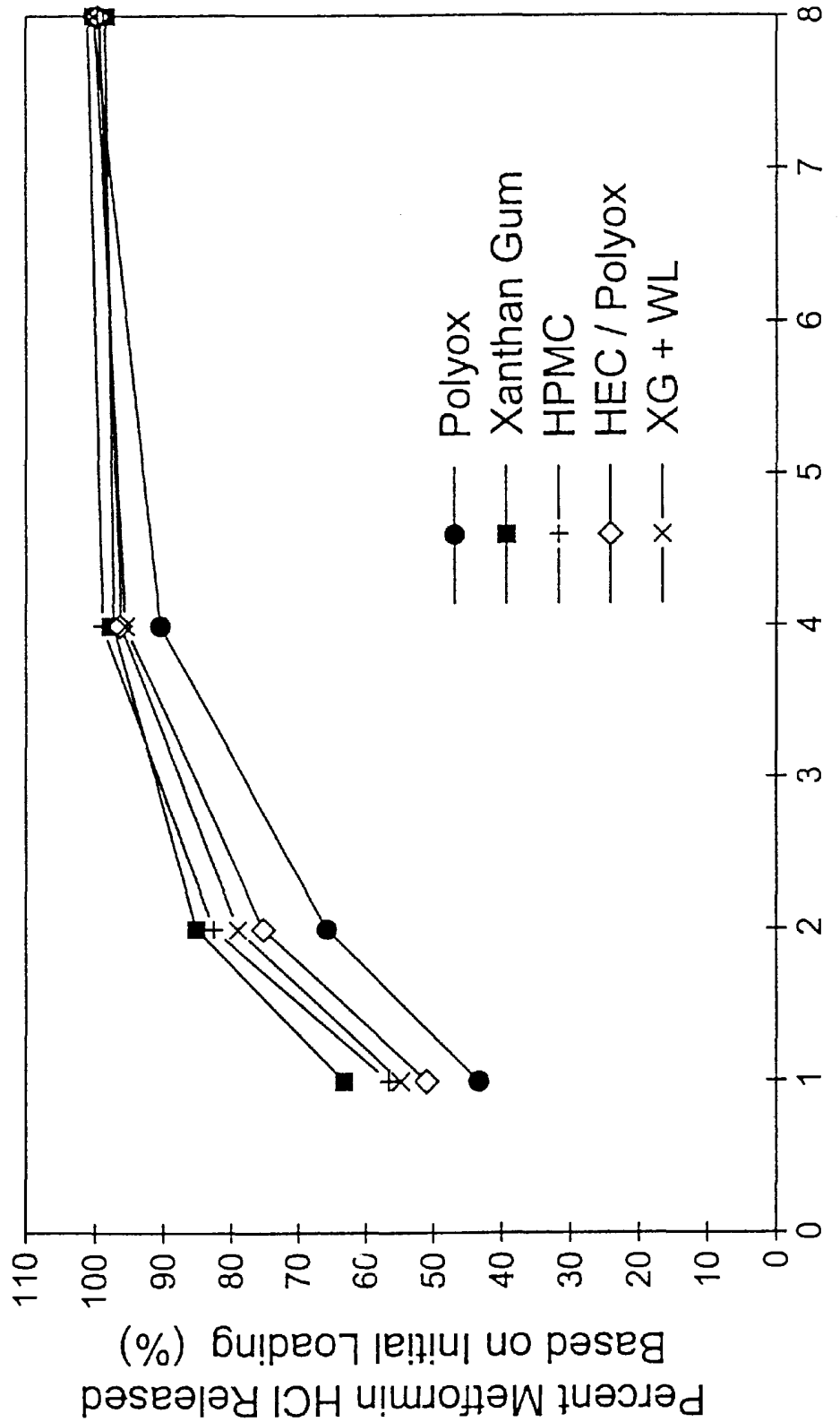

Percent Metformin HCl Released
Based on Initial Loading (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hr)
Polyox
Xanthan Gum
HPMC
HEC / Polyox
XG + WL

Fig. 4

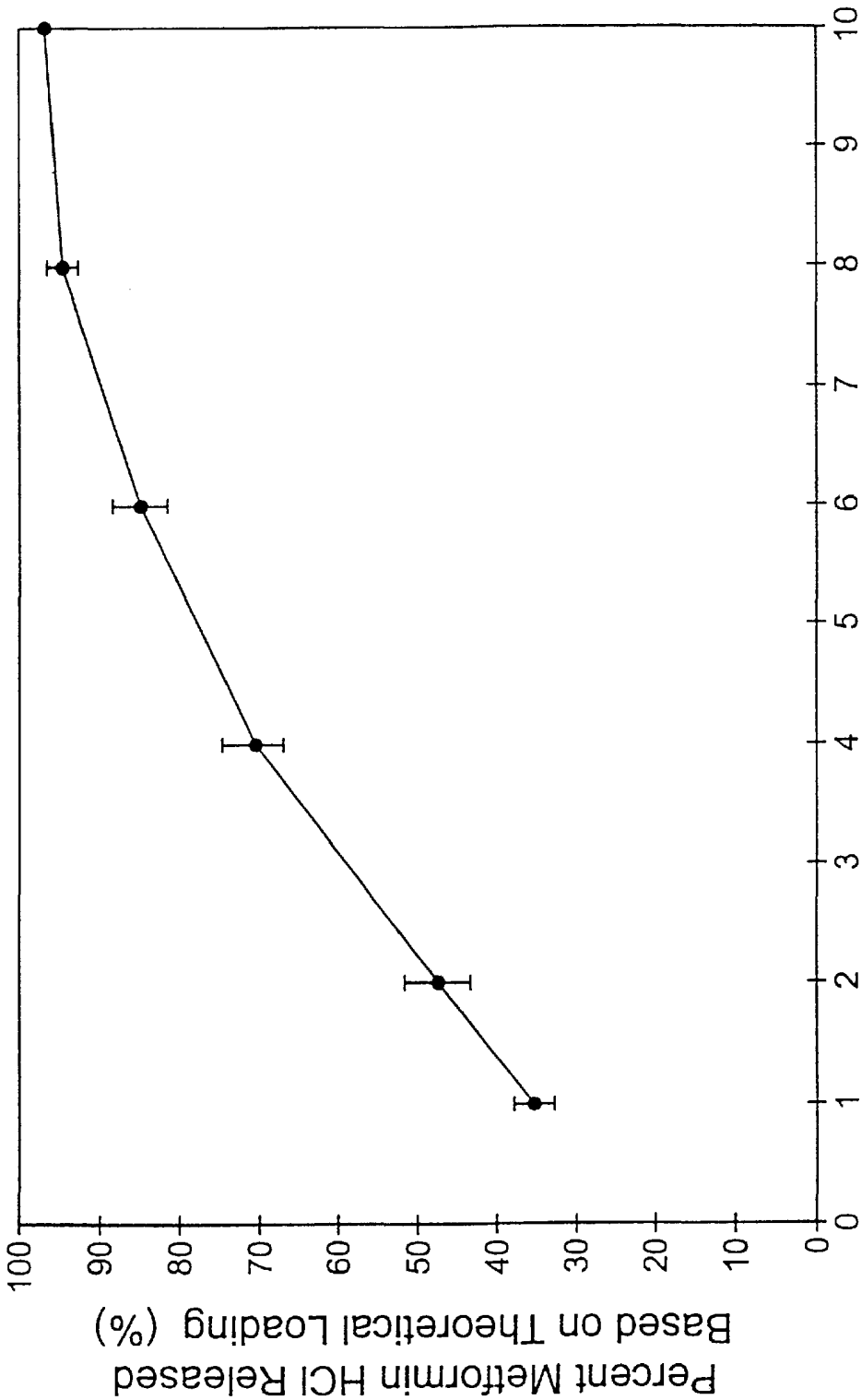

Percent Metformin HCl Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)

Fig. 5

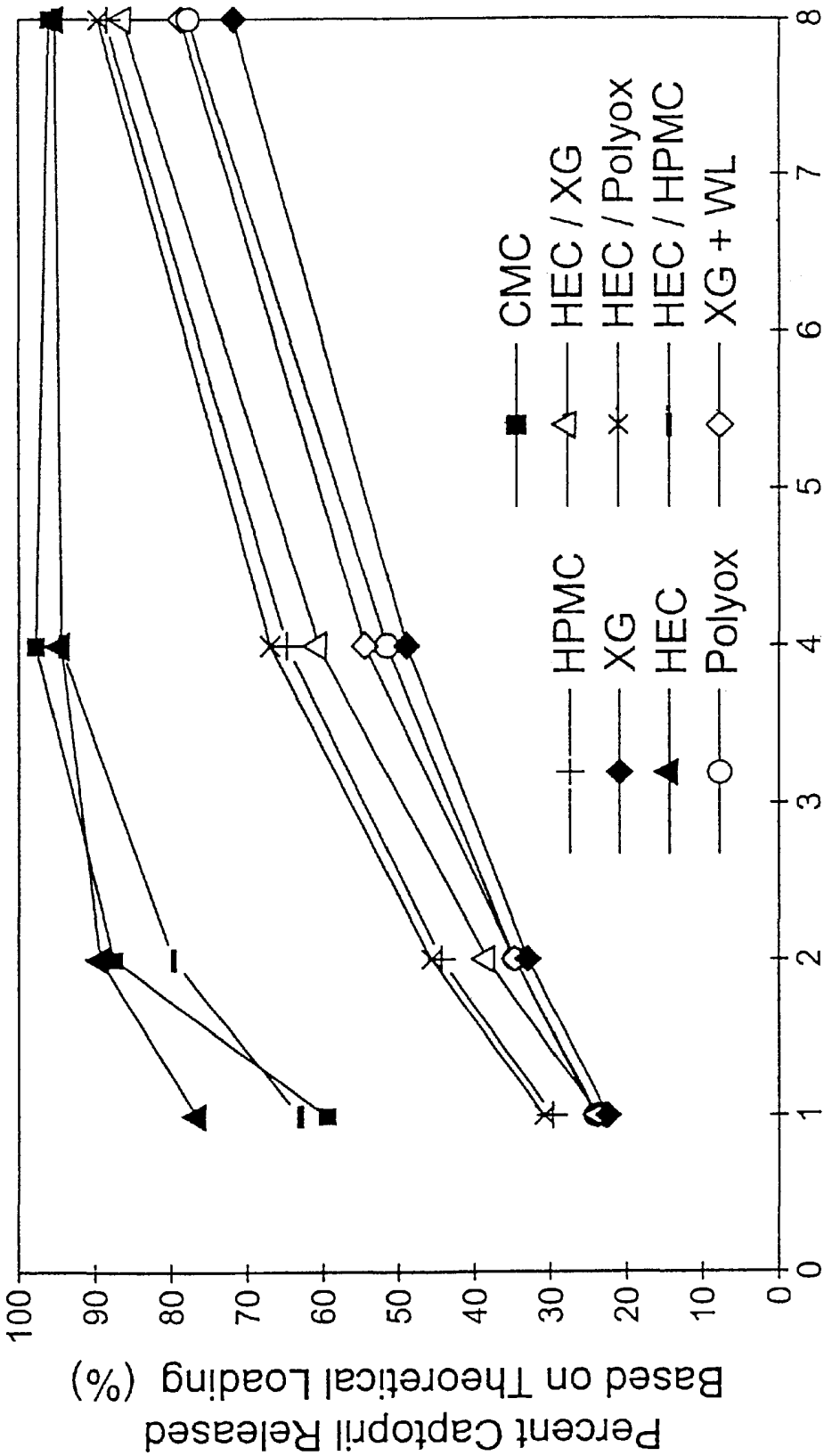

Percent Captopril Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hr)
CMC
HEC / XG
HEC / Polyox
HEC / HPMC
XG + WL
HPMC
XG
HEC
Polyox

Fig. 6

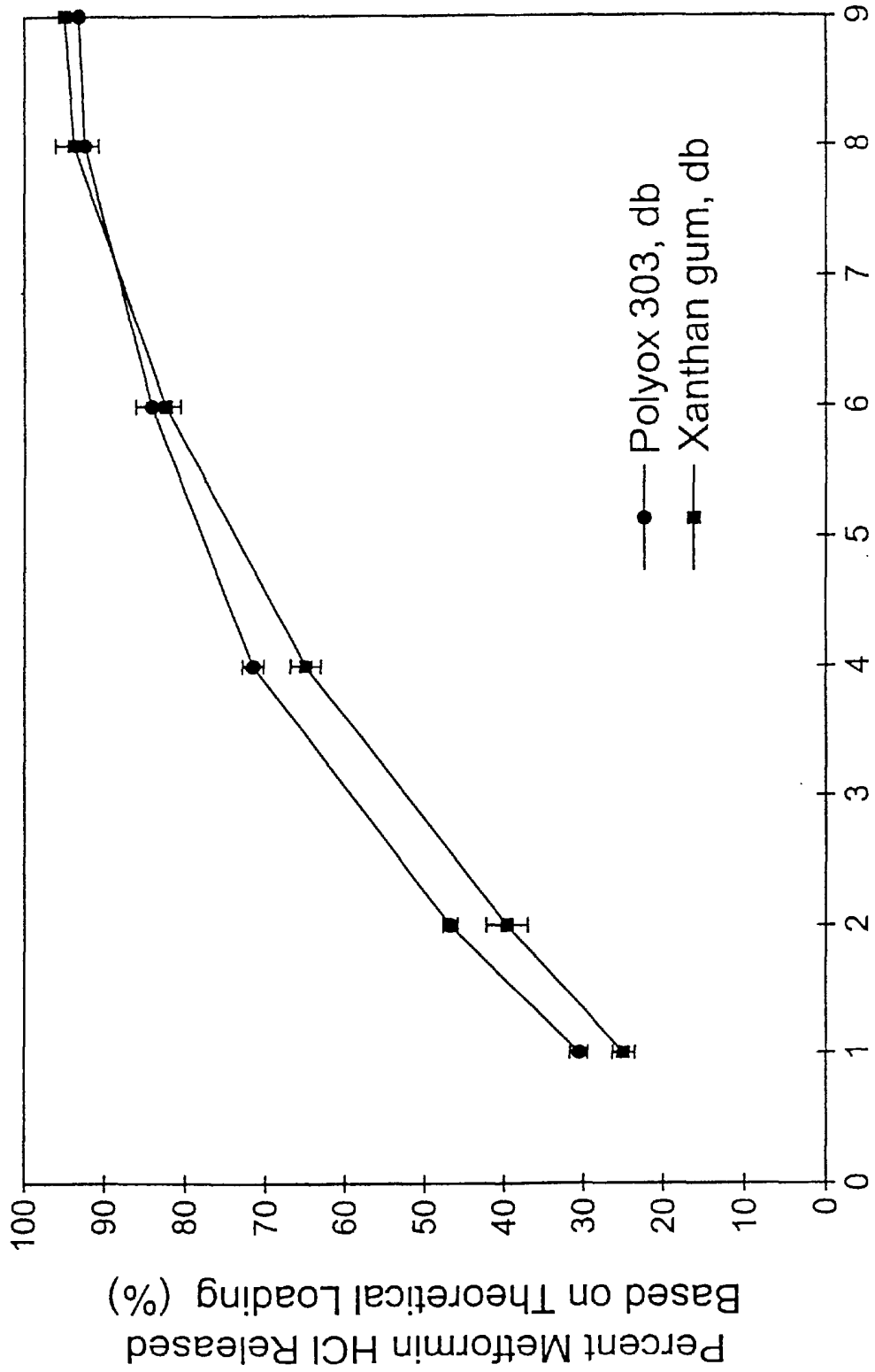

Percent Metformin HCl Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (hr)
Polyox 303, db
Xanthan gum, db

Fig. 7

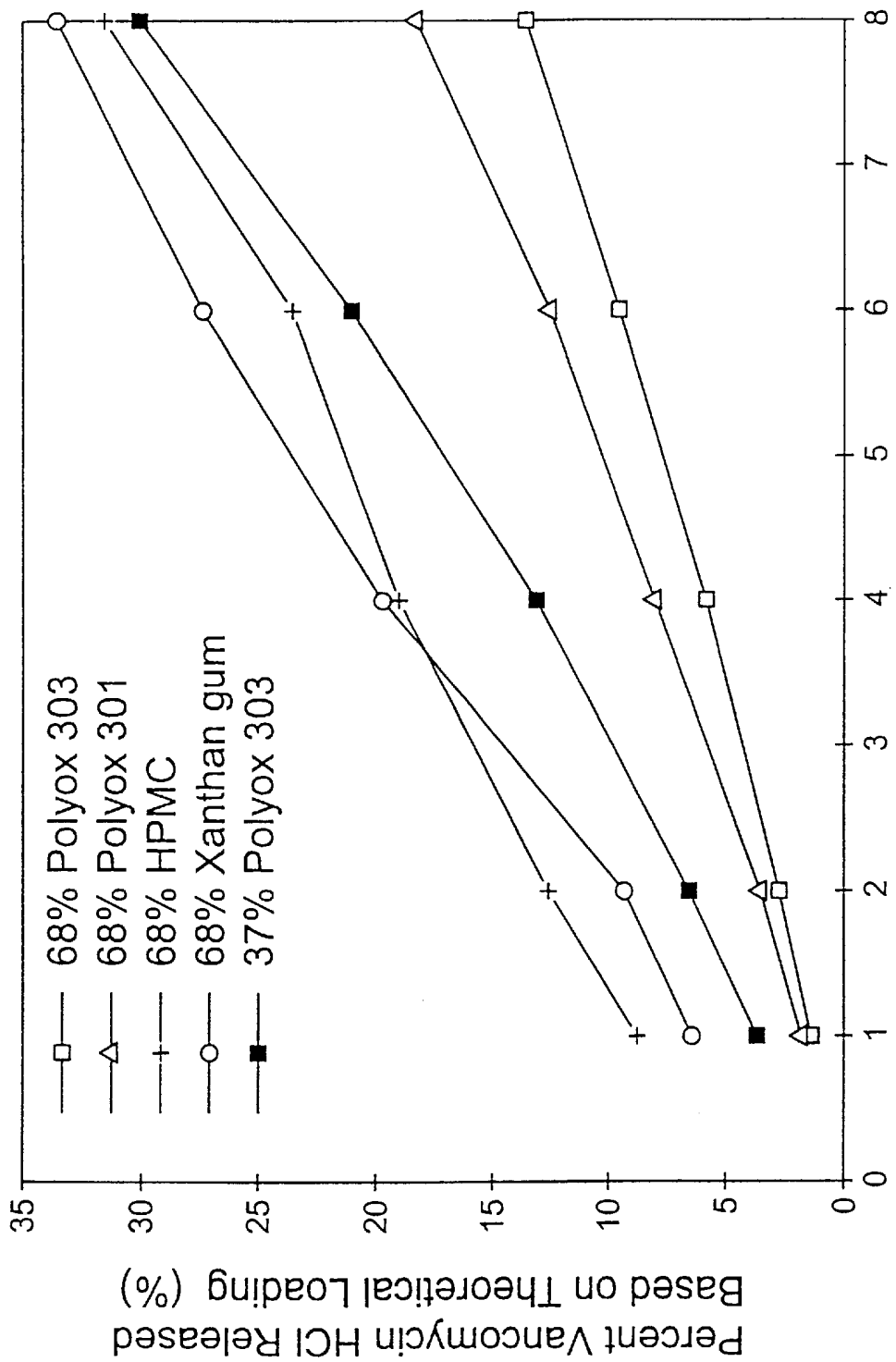
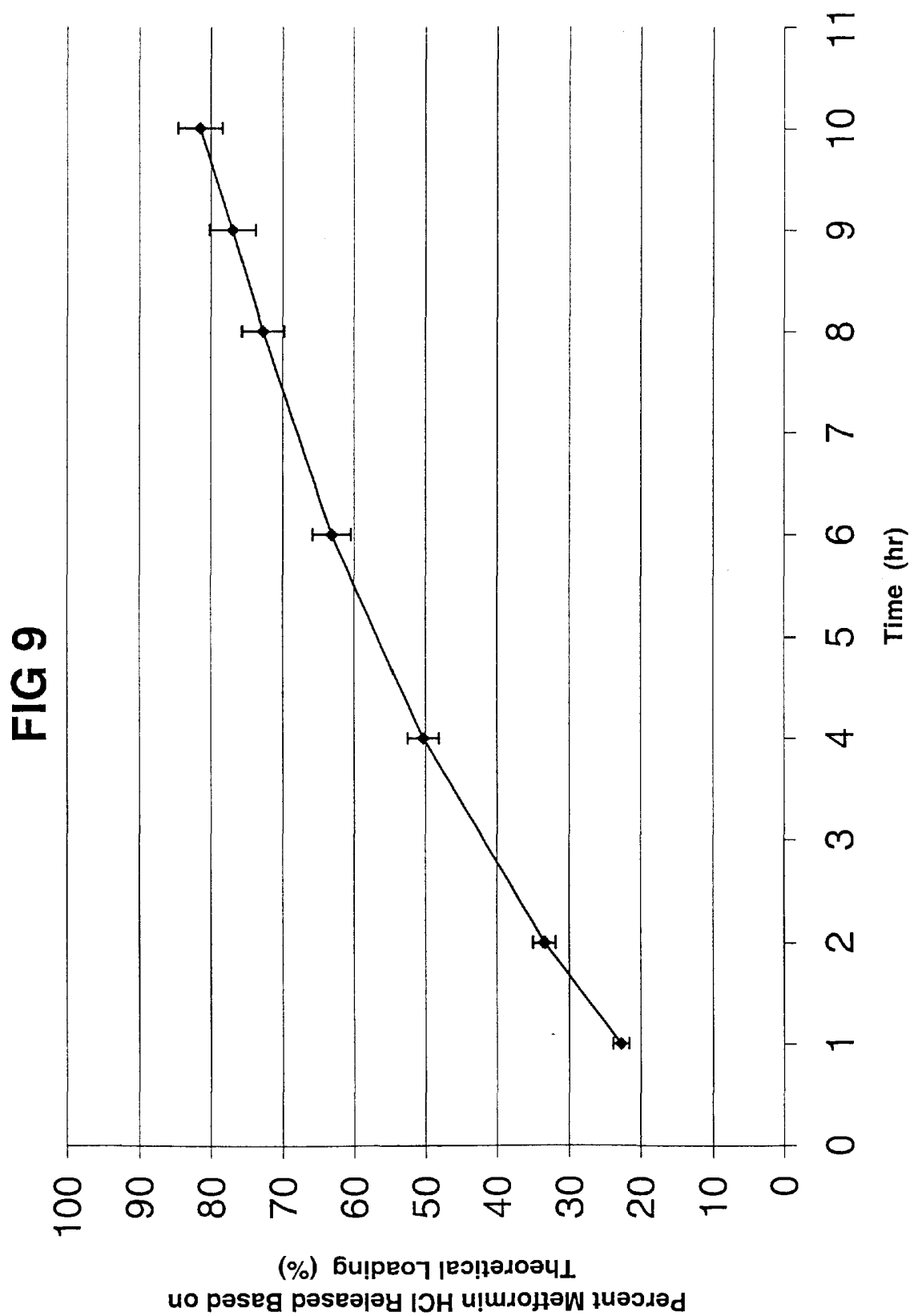

Percent Vancomycin HCl Released
Based on Theoretical Loading (%)
Time (hr)
68% Polyox 303
68% Polyox 301
68% HPMC
68% Xanthan gum
37% Polyox 303
0
5
10
15
20
25
30
35
0
1
2
3
4
5
6
7
8

Fig. 8

FIG 9


Percent Metformin HCl Released Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
Time (hr)

EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 08/870,509, filed Jun. 6, 1997 now abandoned, the entire contents of which are hereby incorporated herein by reference.

This invention is in the general field of pharmacology, and relates in particular to formulations for drugs that benefit from a prolonged time of controlled release in the stomach and upper gastrointestinal (GI) tract, and from an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. One goal in this invention is to release highly soluble drugs in a controlled manner over an extended period of time. Another goal is to extend the time of delivery into the stomach of drugs that are preferentially absorbed high in the GI tract, for purposes of achieving a greater and more prolonged therapeutic effect and thus reducing the frequency of administration required; a more efficient use of the drugs; and a more effective treatment of local stomach disorders. Another goal is to minimize both lower-tract inactivation of the drug and drug effects on the lower intestinal flora by confining the delivery and absorption of the drug to the upper GI tract.

BACKGROUND OF THE INVENTION

Drugs that are administered in the form of conventional tablets or capsules become available to body fluids at a rate that is initially very high, followed by a rapid decline. For many drugs, this delivery pattern results in a transient overdose, followed by a long period of underdosing. This is a pattern of limited clinical usefulness. The delivery pattern was improved in the 1970's with the introduction of a variety of controlled delivery systems. By providing relatively constant, controlled drug delivery, these systems avoided the overdose and the underdose effects. These improvements provided effective medication with reduced side effects, and achieved these results with reduced dosing frequency.

Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrices do not provide adequate control over the drug release rate, instead resulting in a release that approximates first-order kinetics. That is, the rate of release is an inverse function of the square root of the elapsed time. With this pattern of release, most of the drug in the matrix is often released within the first hour in an aqueous medium.

One method of prolonging the release of a highly water-soluble drug is disclosed in International Patent Application Publication No. WO 96/26718, published Sep. 6, 1996 (applicant: Temple University; inventor: Kim). The method of this publication is the incorporation of the drug into a polymeric matrix to form a tablet that is administered orally. The polymer is water-swellable yet erodible in gastric fluids, and the polymer and the proportion of drug to polymer are chosen such that:

(i) the rate at which the polymer swells is equal to the rate at which the polymer erodes, so that the swelling of the polymer is continuously held in check by the erosion, and zero-order release kinetics (constant delivery rate) of the drug from the matrix are maintained;

(ii) the release of drug from the matrix is sustained over the full erosion period of the polymer, the tablet therefore reaching complete solution at the same time that the last of the drug is released; and

(iii) release of the drug from the matrix will be extended over a period of 24 hours.

A key disclosure in WO 96/26718 is that to achieve the release of drug in this manner requires the use of a low molecular weight polymer. If, by contrast, a high molecular weight polymer is used and the swelling rate substantially exceeds the erosion rate, the lack of erosion will prolong even further the delivery of the drug residing close to the center of the tablet and even prevent it from being released. Thus, there is no disclosure in WO 96/26718 that a drug of high water solubility can be released from a high molecular weight polymer in a period of time substantially less than 24 hours, or that any advantage can be obtained by the use of a polymer that does not erode as quickly as it swells. This failure is particularly significant since even swollen tablets will not remain in the stomach beyond the duration of the fed mode, which typically lasts for only 4 to 6 hours.

For drugs of any level of solubility, the retention of the drug in a tablet or other dosage form beyond the duration of the fed mode raises a number of problems that detract from the therapeutic efficacy of the drug. These problems arise from the tendency of the tablet when the patient is no longer in the fed mode to pass from the stomach into the small intestine, and over a period of 2–4 hours to pass through the small intestine, thus reaching the colon with the drug still in the tablet. This loss of effectiveness occurs with drugs that provide their maximum benefit with minimum side effects when absorbed in the stomach and upper GI tract rather than the colon. The reasons are either favorable conditions in the stomach, unfavorable conditions in the colon, or both.

For example, most orally administered antibiotics have a potential of altering the normal flora of the gastrointestinal tract, and particularly the flora of the colon. One result of these alterations is the overgrowth of the organism *Clostridium difficile,* which is a serious adverse event since this organism releases dangerous toxins. These toxins can cause pseudomembranous colitis, a condition that has been reported as a side effect of the use of many antibiotics. In its milder forms, pseudomembranous colitis can cause mild nausea and diarrhea while in its stronger forms, it can be life-threatening or fatal. Examples of highly soluble antibiotics that pose this type of threat are amoxicillin, cefuroxime axetil, and clindamycin. Cefuroxime axetil (i.e., the axetil ester of cefuroxime), for example, becomes active when hydrolyzed to free cefuroxime, but when this occurs prior to absorption, it can be detrimental to essential bacterial flora. Hydrolysis to the active form typically occurs in the tissues into which the ester has been absorbed, but if the ester reaches the lower intestine, enzymes in the lower intestine cause the hydrolysis to occur in the intestine itself, which not only renders the drug unabsorbable but also converts the drug to the active form where its activity alters the flora. Examples of sparingly soluble antibiotics that pose the same type of threat are clarithromycin, azithromycin, ceftazidine, ciprofloxacin, and cefaclor.

A goal of the present invention is to avoid this type of alteration of the lower intestinal flora by delivering antibiotics, regardless of their level of solubility, in a manner that confines their delivery to the stomach and upper small intestine. Slow, continuous delivery from a gastric retentive system assures that both drug delivery and drug absorption are confined to the upper GI tract. More efficient delivery of antibiotics will also avoid transient overdosing which is a major cause of overgrowth of *Clostridium difficile.*

Another example is the class of drugs that are susceptible to degradation by exposure to gastric fluid, either by enzymes or low solution pH. The swellable hydrophilic matrix of the present invention protects the yet undelivered drug during the 4 to 6 hour delivery period during which the drug is continuously released while the dosage form is retained in the stomach. One example of such a drug is topiramate, a drug that is used for the treatment of epilepsy. Topiramate is absorbed preferentially high in the GI tract and is hydrolyzed by the acidic environment of the stomach. The dosage form and delivery system of the present invention will confine the delivery of the drug to the stomach and duodenum. As the drug diffuses out of the swollen matrix, it is susceptible to the acidic environment, but the undelivered drug is protected from degradation by the polymer matrix.

Another example is the class of drugs that are known to have an absorption window high in the GI tract, but are incompletely absorbed or have a wide absorption range, intrapatient as well as interpatient. One example of such a drug is cyclosporine, a drug of low solubility that is used as an immunosuppressant to reduce organ rejection in transplant surgery. In addition to this problem, cyclosporine is in general only incompletely absorbed (on the average around 30%), and the degree of absorption is highly variable from one patient to the next (ranging from about 5% to about 89%). The variability can be attributed in part to differences among the various disease states existing in the patients to whom the drug is administered, and differences in the length of time between the transplant surgery and the administration of the drug. The variability can also however be attributed to the poor aqueous solubility of the drug and to variations in the gastric emptying, variations in the length of time required for intestinal transit between the stomach and the colon, variations in mesenteric and hepatic blood flow, variations in lymph flow, variations in intestinal secretion and fluid volume, variations in bile secretion and flow, and variations in epithelial cell turnover. All of these variations are addressed by the dosage form and delivery system of the present invention, which by confining drug delivery to the stomach reduces these differences and maximizes the absorption of the cyclosporine.

Another example is the class of drugs that are susceptible to degradation by intestinal enzymes. The degradation occurs before the drug can be absorbed through the intestinal wall, leaving only a fraction of the administered dose available for the intended therapeutic action.

An example of a highly soluble drug that is susceptible to degradation by intestinal enzymes is the pro-drug doxifluridine (5'-deoxy-5-fluouridine (dFUR)). The activity of doxifluridine depends on its activation to 5-fluorouracil by pyrimidine nucleoside phosphorylases. These enzymes are found in tumors as well as in normal tissues, with their highest activity being in the small intestine. The activity of these enzymes in tumor cells is more than twice that of normal tissues. When doxifluridine is administered orally, it can be converted to 5-fluorouracil in the intestine before it reaches the tumors. 5-Fluorouracil is much more toxic than doxifluridine and causes intestinal toxicity (nausea and diarrhea) and severe damage to the intestinal villi. A goal of the present invention is to confine the absorption of doxifluridine to the stomach and upper GI tract, thereby avoiding or reducing its conversion to 5-fluorouracil and the attendant toxicity risk. A similar result is sought for other drugs with similar susceptibilities, such as cyclosporine and digoxin.

Another class of drugs whose effectiveness suffers when the drugs are not fully absorbed high in the GI tract are those that are susceptible to inactivation by drug transporters that

reside in lower gastrointestinal tract enterocytes. The inactivation occurs before the drug penetrates the intestinal wall, here again leaving only a fraction of the administered dose available for the intended therapeutic action. One example of a drug transporter is the p-glycoprotein efflux system, in which a p-glycoprotein acts as an absorption barrier to certain drugs that are substrates for the p-glycoprotein. The barrier acts by attaching to these drugs and transporting them drug back into the lumen, e.g., the stomach, duodenum, jejunum/ileum or colon, from which they were absorbed, or preventing them from being absorbed at all. This restriction of the drug to the interior of the GI tract is effectively an inactivation of the drug if the drug must pass out of the GI tract into the bloodstream to be effective. The p-glycoprotein effiux system is useful in many respects, such as preventing toxic compounds from entering the brain. It interferes however in some cases with the efficacy of certain drugs that would otherwise be absorbed. The p-glycoprotein concentration is lowest in the stomach and increases in concentration down the GI tract to the colon where the p-glycoprotein is most prevalent. The dosage form of the present invention will release the drug over an extended period into the upper GI tract where p-glycoprotein is lowest.

Cyclosporine is an example of a drug of low solubility that is susceptible to inactivation by the p-glycoprotein effiux system, in addition to its susceptibility to degradation by colonic bacterial enzymes. Other examples of drugs of low solubility that are susceptible to the p-glycoprotein effiux system are the anti-cancer drug paclitaxel, ciprofloxacin, and the HIV protease inhibitors saquinavir, ritonavir, and nelfinavir. All of these drugs will benefit through preserved activity by the present invention.

A still further class of drugs that suffer in effectiveness when not fully absorbed before reaching the colon are drugs that require an acidic environment for effective bioavailability. For certain drugs, the pH at a given site within the GI tract is an essential determinant of the bioavailability of the drug, since the solubility of the drug varies with pH. The stomach has a low pH and hence an acidic environment, while the small intestine has a higher pH and hence an alkaline environment. Higher bioavailability is achieved in some cases by higher solubility, which with some drugs occurs in a more acidic environment, and in other cases by keeping the drugs in a non-ionized state that is necessary for absorption, which with some drugs also occurs in a more acidic environment. Acidic drugs that have a low pK, for example, are in the neutral form that is required for absorption and are therefore preferentially absorbed in the stomach. Examples of highly soluble drugs that achieve their highest bioavailability at a low pH are esters of ampicillin. Examples of low solubility drugs that behave similarly are iron salts, digoxin, ketoconazole, fluconazole, griseofulvin, itraconazole, and micoconazole. A further goal of the present invention is therefore to maximize the bioavailability of drugs of these types by confining them to the acidic environment of the stomach while controlling their release rate to achieve an extended release profile. The invention thus improves the efficiency of iron salts in the treatment of the various forms of anemia, the efficiency of digoxin in the treatment of the heart disease, and the efficiency of ketoconazole in the treatment of systemic fungal infections such as candidiasis, canduria, blastomycosis, coccidiomycosis, histoplasmosis, chronomycosis, and pacococcidiomycosis.

The invention also improves the efficiency of drugs that have at least one ionized group in the pH range of 5 through 8. Since this is the pH range encountered in the small

intestine and the region of the colonic junction and ionized drugs are less absorbable than neutral drugs, this invention improves the absorption of these drugs by retaining them in the stomach environment. The invention also improves the efficiency of drugs that are degradable in an acidic environment such as that of the stomach by protecting them from the acidic environment until they are released from the dosage form, thereby reducing the duration of their exposure to the acidic environment.

A still further example of drugs that lose their efficacy upon reaching the lower portions of the GI tract are drugs that are soluble in an acidic environment but insoluble in an alkaline environment. The HIV protease inhibitor nelfinavir mesylate is one example of such a drug. Portions of the drug that are undissolved cannot be absorbed. Portions that are dissolved but not yet absorbed when they pass from the stomach into the small intestine may undergo precipitation and loss of their therapeutic benefit. This is confirmed by the fact that the presence of food in the GI tract substantially increases the extent of absorption of oral nelfinavir. Peak plasma concentration and area under the plasma concentration-time curve of nelfinavir are two-fold to three-fold greater when doses are administered with or following a meal. This is presumably due, at least in part, to enhanced retention of the drug in the stomach. A further goal of the present invention is therefore to provide a means of administering these drugs that will maximize their therapeutic effectiveness by extended, controlled release into the stomach.

SUMMARY OF THE INVENTION

It has now been discovered that drugs that are highly soluble in water can be administered orally in a manner that will prolong their delivery time to spread their release rate more evenly throughout the duration of the fed mode and beyond or not as desired. This significantly reduces, and often avoids, the problems of transient overdosing caused by the initial spike in concentration entering the blood stream immediately after administration and the subsequent underdosing, and instead controls the dosage to safer and more effective levels over an extended period of time.

It has further been discovered that for drugs of high, intermediate or low solubility, the problems arising from the release of the drugs in the lower GI tract, i.e., from the failure to absorb these drugs into the blood stream prior to reaching the lower GI tract, can be mitigated as well. For all drugs regardless of solubility, therefore, this invention corrects problems such as the overgrowth of detrimental intestinal flora by drugs that are toxic to normal intestinal flora, protection of undelivered acid-labile drugs in the dosage form, chemical degradation of drugs by intestinal enzymes, loss of bioavailability of the drugs due to their leaving the acidic environment of the stomach, and chemical degradation of the drugs due to the alkaline environment of the intestinal tract. By mitigating these problems, this invention thus further improves the efficiency of the use of these drugs.

Each of the beneficial effects enumerated above is achieved by using a formulation in which the drug is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the drug primarily by diffusion. It has further been found that the rate of diffusion of the drug out of the matrix can be slowed by increasing the drug particle size, by the choice of polymer used in the matrix, and/or by the choice of molecular weight of the polymer. The matrix is a relatively high molecular weight polymer that swells upon ingestion, preferably to a size that is at least about twice its unswelled volume, and that promotes gastric retention during the fed mode. Upon swelling, the matrix may also convert over a prolonged period of time from a glassy polymer to a polymer that is rubbery in consistency, or from a crystalline polymer to a rubbery one. The penetrating fluid then causes release of the drug in a gradual and prolonged manner by the process of solution diffusion, i.e., dissolution of the drug in the penetrating fluid and diffusion of the dissolved drug back out of the matrix. The matrix itself is solid prior to administration and, once administered, remains undissolved in (i.e., is not eroded by) the gastric fluid for a period of time sufficient to permit the majority of the drug to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of the drug is therefore controlled diffusion of the drug from the matrix rather than erosion, dissolving or chemical decomposition of the matrix.

For highly soluble drugs, the swelling of the polymeric matrix thus achieves two objectives—(i) the tablet swells to a size large enough to cause it to be retained in the stomach during the fed mode, and (ii) it retards the rate of diffusion of the highly soluble drug long enough to provide multi-hour, controlled delivery of the drug into the stomach. For drugs that are either sparingly soluble, of limited solubility, or of high solubility, and that experience any of the specific problems enumerated above upon reaching the lower GI tract prior to absorption into the bloodstream, the swelling of the polymeric matrix (i) renders the matrix sufficiently large to cause retention in the stomach during the fed mode, and (ii) localizes the release of the drug to the stomach and small intestine so that the drug will have its full effect without colonic degradation, inactivation, or loss of bioavailability.

In either of these aspects, the invention provides an effective means of using these drugs to treat local stomach disorders as well as a wide variety of disease conditions. For example, use of this invention provides more effective eradication of ulcer-causing bacteria in the gastric mucosa with soluble antibiotics. The invention also provides enhanced absorption of soluble drugs that are absorbed mostly in the stomach or high in the gastrointestinal tract, such as metformin hydrochloride or ciprofloxacin. The invention is also useful in providing a multi-hour flow of a drug past the upper part of the small intestine (the most efficient absorption site for many agents).

Details of these and other features of the invention will be apparent from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plot showing the release rate of metformin hydrochloride from three different compositions of the drug in poly(ethylene oxide) matrices.

FIG. **2** is a plot showing the release rate of captopril from a poly(ethylene oxide) matrix, in accordance with this invention, both with and without glyceryl monostearate as a solubility modifier.

FIG. **3** is a plot showing the release rate of captopril from hydroxyethyl cellulose, in which the pellet size was varied.

FIG. **4** is a plot showing the release rate of metformin hydrochloride from various polymeric matrices.

FIG. **5** is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

FIG. **6** is a plot showing the release rate of captopril from various polymeric matrices.

FIG. **7** is a plot showing further release rate studies of metformin hydrochloride from two different polymeric matrices.

FIG. **8** is a plot showing the release rate of vancomycin hydrochloride from different polymeric matrices.

FIG. **9** is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

In aspects of this invention that are directed to highly soluble drugs, the drugs thus addressed are those that are characterized by the United States Pharmacopeia XXII as at least "freely soluble" in water, i. e., drugs whose solubility is greater than one part of the drug in about ten parts of water. Drugs of particular interest are those whose solubility is greater than one part in about five parts of water, and drugs of even greater interest are those whose solubility is greater than one part in about three parts of water. The parts referred to in this paragraph and throughout this specification are parts by weight.

The term "drug" is used herein to denote any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a therapeutic effect in the treatment of a disease or abnormal physiological condition. Examples of drugs of high solubility to which this invention is applicable are metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, doxifluridine, tramadol, fluoxitine hydrochloride, ciprofloxacin, gancyclovir, bupropion, lisinopril, and esters of ampicillin. Examples of drugs of low solubility to which this invention is applicable are cefaclor, ciprofloxacin, saguinavir, ritonavir, nelfinavir, clarithromycin, azithromycin, ceftazidine, cyclosporin, digoxin, paclitaxel, iron salts, topiramate, and ketoconazole. Other drugs suitable for use and meeting the solubility criteria described above will be apparent to those skilled in the art. Drugs of particular interest are metformin hydrochloride and sertraline hydrochloride. The drug loadings (weight percent of drug relative to total of drug and polymer) in most of these cases will be about 80% or less.

The invention is also of use with drugs that have been formulated to include additives that impart a small degree of hydrophobic character, to further retard the release rate of the drug into the gastric fluid. One example of such a release rate retardant is glyceryl monostearate. Other examples are fatty acids and salts of fatty acids, one example of which is sodium myristate. The quantities of these additives when present can vary; and in most cases, the weight ratio of additive to drug will range from about 1:20 to about 1:1, and preferably from about 1:8 to about 1:2.

The water-swellable polymer forming the matrix in accordance with this invention is any polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of an incorporated drug. Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone), starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly (ethyleneimine), polyurethane hydrogels, and crosslinked polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers. Specific examples of copolymers are PLURONIC® and TECTONIC®, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA.

The terms "cellulose" and "cellulosic" are used herein to denote a linear polymer of anhydroglucose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C. Particularly preferred alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

Polyalkylene oxides of greatest utility in this invention are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Poly(ethylene oxide) polymers having molecular weights of about 4,000,000 and higher are preferred. More preferred are those with molecular weights within the range of about 4,500,000 to about 10,000,000, and even more preferred are polymers with molecular weights within the range of about 5,000,000 to about 8,000,000. Preferred poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about 1×10^5 to about 1×10^7, and preferably within the range of about 9×10^5 to about 8×10^6. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For purposes of this invention, a preferred viscosity range is about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20° C. Two presently preferred poly(ethylene oxide)s are POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamsan gum. Xanthan gum is preferred.

Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Preferred crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25° C. Three presently preferred examples are CARBOPOL® NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples are polymers known as WATER LOCK®, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

The hydrophilicity and water swellability of these polymers cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the drug particle size and the drug concentration in the matrix. Also, because these polymers dissolve very slowly in gastric fluid, the matrix maintains its physical integrity over at least a substantial period of time, in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. Complete dissolution or decomposition may not occur until 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within 10 to 24 hours after the dosing period.

The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 40% of the drug within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 50% of the drug remains in the matrix one hour after ingestion. More preferably, at least 60%, and most preferably at least 80%, of the drug remains in the matrix one hour after ingestion. In all cases, however, the drug will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

The benefits of this invention will be achieved over a wide range of drug loadings, with the weight ratio of drug to polymer ranging in general from 0.01:99.99 to about 80:20. Preferred loadings (expressed in terms of the weight percent of drug relative to total of drug and polymer) are those within the range of 15% to 80%, more preferably within the range of 30% to 80%, and most preferably in certain cases within the range of about 30% to 70%. For certain applications, however, the benefits will be obtained with drug loadings within the range of 0.01% to 80%, and preferably 15% to 80%.

The formulations of this invention may assume the form of particles, tablets, or particles retained in capsules. A preferred formulation consists of particles consolidated into a packed mass for ingestion, even though the packed mass will separate into individual particles after ingestion. Conventional methods can be used for consolidating the particles in this manner. For example, the particles can be placed in gelatin capsules known in the art as "hard-filled" capsules and "soft-elastic" capsules. The compositions of these capsules and procedures for filling them are known among those skilled in drug formulations and manufacture. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested.

In certain embodiments of this invention, the formulation contains an additional amount of the drug applied as a quickly dissolving coating on the outside of the particle or tablet. This coating is referred to as a "loading dose" and it is included for immediate release into the recipient's bloodstream upon ingestion of the formulation without first undergoing the diffusion process that the remainder of the drug in the formulation must pass before it is released. The "loading dose" is high enough to quickly raise the blood concentration of the drug but not high enough to produce the transient overdosing that is characteristic of highly soluble drugs that are not formulated in accordance with this invention.

One presently preferred dosage form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, 6.6 or 6.7 mm (or more generally, 6.5 to 7 mm) in diameter and 9.5 or 10.25 mm (or more generally, 9 to 12 mm) in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6.6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.25 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 7.5 mm in length. Another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 10 mm in width, and 5 to 7.5 mm in height. Still another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 7.8 mm in width, and 6.2 to 7.5 mm in height. A preferred set of dimensions is 20 mm in length, 6.7 mm in width, and 6.4 mm in height. These are merely examples; the shapes and sizes can be varied considerably.

The particulate drug/polymer mixture or drug-impregnated polymer matrix can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such techniques are as follows:

(1) Direct compression, using appropriate punches and dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pa., USA; the punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pa., USA;

(2) Injection or compression molding using suitable molds fitted to a compression unit, such as those available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.;

(3) Granulation followed by compression; and

(4) Extrusion in the form of a paste, into a mold or to an extrudate to be cut into lengths.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the particle) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight,

preferably less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular drug, including both its pharmacological characteristics and its physical characteristics such as solubility, and with the characteristics of the swellable matrix such as its permeability, and the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight hours or more, preferably once every twelve hours or more, and even more preferably once every twenty-four hours or more.

As indicated above, the dosage forms of the present invention find their greatest utility when administered to a subject who is in the digestive state (also referred to as the postprandial or "fed" mode). The postprandial mode is distinguishable from the interdigestive (or "fasting") mode by their distinct patterns of gastroduodenal motor activity, which determine the gastric retention or gastric transit time of the stomach contents.

In the interdigestive mode, the fasted stomach exhibits a cyclic activity called the interdigestive migrating motor complex (IMMC). The cyclic activity occurs in four phases:

- Phase I is the most quiescent, lasts 45 to 60 minutes, and develops few or no contractions.
- Phase II is marked by the incidence of irregular intermittent sweeping contractions that gradually increase in magnitude.
- Phase III, which lasts 5 to 15 minutes, is marked by the appearance of intense bursts of peristaltic waves involving both the stomach and the small bowel.
- Phase IV is a transition period of decreasing activity which lasts until the next cycle begins.

The total cycle time is approximately 90 minutes, and thus, powerful peristaltic waves sweep out the contents of the stomach every 90 minutes during the interdigestive mode. The IMMC may function as an intestinal housekeeper, sweeping swallowed saliva, gastric secretions, and debris to the small intestine and colon, preparing the upper tract for the next meal while preventing bacterial overgrowth. Pancreatic exocrine secretion of pancreatic peptide and motilin also cycle in synchrony with these motor patterns.

The postprandial or fed mode is induced by food ingestion, and begins with a rapid and profound change in the motor pattern of the upper GI tract, the change occurring over a period of 30 seconds to one minute. The stomach generates 3–4 continuous and regular contractions per minute, similar to those of the interdigestive mode but of about half the amplitude. The change occurs almost simultaneously at all sites of the GI tract, before the stomach contents have reached the distal small intestine. Liquids and small particles flow continuously from the stomach into the intestine. Contractions of the stomach result in a sieving process that allows liquids and small particles to pass through a partially open pylorus. Indigestible particles greater than the size of the pylorus are retropelled and retained in the stomach. Particles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours. The dosage form of the present invention is designed to achieve the minimal size through swelling following ingestion during the fed mode.

The following examples are offered for purposes of illustration, and are not intended to limit the invention in any manner.

EXAMPLE 1

This example illustrates the controlled-release behavior of metformin hydrochloride, a highly soluble drug (whose solubility is approximately 30%), from a polymeric matrix consisting of poly(ethylene oxide). Three different dose levels were prepared—systems designed to release 90% of their drug contents at approximately 3 hours, 6 hours, and 8 hours, respectively.

Drug and polymer, with 0.5% magnesium stearate as a tableting lubricant, were compressed into pellets measuring 7.2 mm diameter×8.8 mm length and weighing 390 mg for samples designed for 3-hour and 6-hour release, and 7.4 mm diameter×8.5 mm length and weighing 380 mg for samples designed for 8-hour release, and two pellets of a given type were incorporated into a single gelatin capsule. Thus, three different types of gelatin capsule were prepared as follows:

$t_{90\%} \cong$ 3 hours	
metformin hydrochloride	250.00 mg
POLYOX ® 1105, molecular weight 900,000	138.67
magnesium stearate	1.95
Total	390.62 mg
$t_{90\%} \cong$ 6 hours	
metformin hydrochloride	250.00 mg
POLYOX ® Coagulant, molecular weight 5,000,000	138.67
magnesium stearate	1.95
Total	390.62 mg
$t_{90\%} \cong$ 8 hours	
metformin hydrochloride	125.00 mg
POLYOX ® 303, molecular weight 7,000,000	266.11
magnesium stearate	1.97
Total	393.08 mg

Release rate tests on each of these three formulations were performed in modified artificial gastric fluid by the following procedure.

Dissolution was performed in a USP Apparatus 2, modified to include a stainless steel cone (⅞ inch in height and ⅞ inch in diameter at the base) at the bottom of each vessel, placed directly beneath the paddle shaft to eliminate the "dead zone" effect. A paddle speed of 60 rpm and a bath temperature of 37.4° C. were used. The gelatin capsule was opened and the individual pellets and empty gelatin capsule were dropped into the dissolution vessel containing 900 mL of modified simulated gastric fluid (7 mL of hydrochloric acid and 2 g of sodium chloride in 100 mL of deionized water; the enzyme pepsin was omitted). Once the pellets had settled to the bottom of the vessel, the paddle rotation was initiated. Samples 5 mL in size were taken at specified time points, and the sample volumes were not replaced. The samples were diluted as necessary for quantitative analysis by HPLC.

The results are shown in FIG. **1**, where the filled diamonds represent the $t_{90\%}\cong 3$ formulation, the x's represent the $t_{90\%}\cong 6$ formulation, and the open circles represent the $t_{90\%}\cong 8$ formulation. The curves show that the $t_{90\%}$ value of the first formulation was fairly close to 3.5 hours, the $t_{90\%}$ value of the second formulation was fairly close to 6.0 hours, and $t_{90\%}$ value of the third formulation was fairly close to 7.5 hours.

EXAMPLE 2

This example illustrates the controlled-release behavior of captopril from a polymeric matrix consisting of poly (ethylene oxide), both with and without glyceryl monostearate (8% by weight). The formulations used were as follows:

1. Captopril	92.50 mg
Poly(ethylene oxide) (POLYOX ® 301), molecular weight 4,000,000	407.50
Total	500.00 mg
2. Captopril	92.5 mg
glyceryl monostearate	15.0
Poly(ethylene oxide) (POLYOX ® 301), molecular weight 4,000,000	392.5
Total	500.0 mg

Each formulation was compressed into a tablet measuring 6.0 mm diameter×6.7 mm length and weighing 180 mg. Release rate tests on each of the two tablets were performed in modified simulated gastric fluid by the procedure of Example 1, except that the paddle rotation speed was 30 rpm and the tablets were dropped directly into the dissolution vessel.

The results are shown in FIG. **2**, where the filled squares represent Formulation No. 1 consisting of captopril and poly(ethylene oxide) only, and the open circles represent Formulation No. 2 which further contained glyceryl monostearate.

EXAMPLE 3

This example illustrates the controlled-release behavior of captopril from a polymeric matrix of hydroxyethyl cellulose with the inclusion of glyceryl monostearate, but at varying pellet sizes. The formulation contained 19% captopril (all percents by weight) and 4.8% glyceryl monostearate in hydroxyethyl cellulose of molecular weight within the range of 1,000,000 to 1,500,000. The pellet sizes and weights were (a) 3.3 mm diameter×3.5 mm length at 35 mg (referred to herein as 3-mm tablets), (b) 4.3 mm diameter×4.9 mm length at 75 mg (referred to herein as 4-mm tablets), and (c) 6.3 mm diameter×6.5 mm length at 187 mg (referred to herein as 6-mm tablets).

Release rate tests on each of the three tablet sizes (fifteen of the 3-mm tablets, seven of the 4-mm tablets, and three of the 6-mm tablets) were performed using the procedures of Example 1, except that a weighted watchglass was used in place of the stainless steel cone, and analyses of the samples were performed by UV/Vis. The results are shown in FIG. **3**, where the filled squares represent the 3-mm pellets, the filled triangles the 4-mm pellets, and the filled circles the 6-mm pellets. This demonstrates the variation of pellet size as a further means of varying the release pattern, the larger pellets having less surface area.

EXAMPLE 4

This example further illustrates the controlled release of metformin hydrochloride, using a higher drug loading, and various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **4** where the results are plotted, were as follows (all percentages are by weight):

Filled circles: 79.6% metformin HCl; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.04 mm diameter×9.48 mm length; containing approximately 478 mg metformin HCl.

Filled squares: 79.6% metformin HCl; 20% xanthan gum (KELTROL® F, Kelco, Div. of Merck & Co., Inc., San Diego, Calif., USA); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.40 mm length; containing approximately 483 mg metformin HCl.

Plus signs: 79.6% metformin HCl; 20% hydroxypropylmethyl cellulose (BENECEL® 824, Aqualon Co., Wilmington, Del., USA), viscosity (2%, 20° C.) 11,000 to 15,000 cps; 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.49 mm length; containing approximately 480 mg metformin HCl.

Open diamonds: 79.6% metformin HCl; 5% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 15% poly(ethylene oxide (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.60 mm length; containing approximately 480 mg metformin HCl.

x's: 79.6% metformin HCl, 18.05% xanthan gum (KELTROL® F); 1.99% WATER LOCKS D-223 (starch graft poly(2-propenamide-co-2-propenoic acid)), mixed sodium and aluminum salts, Grain Processing Corporation, Muscatine, Iowa, USA); 0.4% magnesium stearate. Pellet dimensions were 6.06 mm diameter×9.24 mm length; containing approximately 476 mg metformin HCl total.

EXAMPLE 5

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **5**. The formulation was as follows (all percentages are by weight): 64% metformin HCl; 35.5% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 6.48 mm diameter×7.20 mm height×19.21 mm length, and contained approximately 506 mg metformin HCl per tablet.

EXAMPLE 6

This example further illustrates the controlled release of captopril, using various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **6** where the results are plotted, were as follows (all percentages are by weight):

Plus signs: 80% captopril; 20% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.03 mm diameter×9.25 mm length, 2 pellets weighing 293 mg each, containing approximately 469 mg captopril total.

Filled diamonds: 80% captopril; 20% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter×9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Filled triangles: 80% captopril; 20% hydroxyethyl cellulose (250HX, molecular weight 1,000,000). Pellet dimensions: 6.03 mm diameter×9.53 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open circles: 80% captopril; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.59 mm length, 2 pellets weighing 301 mg each, containing approximately 482 mg captopril total.

Filled squares: 80% captopril; 20% carboxymethyl cellulose (12M31P, molecular weight 250,000). Pellet dimensions: 6.04 mm diameter×9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open triangles: 79.93% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.04% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter×9.26 mm length, 2 pellets weighing 296 mg each, containing approximately 473 mg captopril total.

x's: 79.96% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.01% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

Dashes: 80% captopril; 10% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 298 mg each, containing approximately 477 mg captopril total.

Open diamonds: 79.96% captopril; 18.05% xanthan gum (KELTROL® F); 1.99% WATERLOCK® D-223. Pellet dimensions: 6.04 mm diameter×9.16 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

EXAMPLE 7

This example presents further data on metformin hydrochloride formulations, illustrating the effect of lower drug loadings than those used in the preceding examples. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **7** where the results are plotted, were as follows (all percentages are by weight):

Filled squares: 32.5% metformin HCl; 67% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions 6.62 mm diameter×10.40 mm length, 2 pellets weighing 400 mg each, containing approximately 260 mg metformin HCl total.

Open circles: 32.5% metformin HCl; 67% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions 6.65 mm diameter×9.28 mm length; 2 pellets weighing 401 mg each, containing approximately 261 mg metformin HCl total.

EXAMPLE 8

This example illustrates the sustained release of vancomycin hydrochloride from various polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **8** where the results are plotted, were as follows (all percentages are by weight):

Open squares: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.23 mm length, 2 pellets weighing 403 mg each, containing approximately 254 mg vancomycin hydrochloride total.

Open triangles: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX® 301, molecular weight 4,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.28 mm length, 2 pellets weighing 402 mg each, containing approximately 253 mg vancomycin hydrochloride total.

x's: 31.5% vancomycin hydrochloride; 68% hydroxypropyl methylcellulose (BENECEL® 824, viscosity 11,000–15,000 cps (2% solution at 20° C.)); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.10 mm length, 2 pellets weighing 405 mg each, containing approximately 255 mg vancomycin hydrochloride total.

Open circles: 31.5% vancomycin hydrochloride; 68% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions: 6.62 mm diameter×9.77 mm length, 2 pellets weighing 401 mg each, containing approximately 253 mg vancomycin hydrochloride total.

Filled squares: 62.5% vancomycin hydrochloride; 37% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.60 mm diameter×10.01 mm length, 2 pellets weighing 409 mg each, containing approximately 511 mg vancomycin hydrochloride total.

In the prior art, vancomycin and its salts are administered by injection, due to poor absorption when administered orally. By providing for all or at least a portion of the total administered amount to be delivered by controlled delivery in the gastric retentive system of this invention, that portion so delivered is directed to the proximal portion of the small intestine, the most efficient site for absorption of this drug, resulting in an enhanced absorption from the oral dosage form of the invention.

EXAMPLE 9

This example illustrates the difference between subjects in the fed mode and subjects not in the fed mode in terms of the gastric retention of tablets of various sizes administered orally. Both Beagle dogs and human subjects were used.

Barium-containing tablets for oral administration were prepared from the following ingredients:

25% Barium Sulfate

30% PolyOx 303 (average molecular weight 7,000,000)

44.5% Hydroxypropylcellulose

0.5% Magnesium Stearate

For tests on Beagle dogs, 400-mg tablets measuring 5.8 mm diameter×5.1 mm height×15.4 mm length were prepared in a tablet press at 2,500 psi pressure, and 800-mg tablets measuring 7.9 mm diameter×5.6 mm height×19.1 mm length were prepared in a tablet press at 5,000 psi. Four beagle dogs were used, and the location of the tablets in the GI tract was followed using fluoroscopy. Two studies were initiated with the dogs. In the first study, each dog received two tablets (one 400-mg and one 800-mg) with a small amount of water after a 16-hour fast. In the second study, each dog received two tablets (one 400-mg and one 800-mg) thirty minutes after ingesting 50 grams of a standard meal. The location of the tablets (in or out of the stomach) was monitored every 30 minutes with the fluoroscope.

The fluoroscopy revealed that tablets that were administered while the dogs were in the fasted condition were emptied from the dogs' stomachs within 90 minutes: in two of the dogs, the stomachs contained no barium tablets at 30 minutes, in a third this was true at 60 minutes, and in the fourth at 90 minutes. Tablets that were administered while the dogs were in the fed state remained in the dogs' stomach for between 4 and 5 hours.

Human tests were performed on ten normal adults of both sexes, each taking part in two trials, the first after fasting and the second after a bacon and egg breakfast of approximately 1,500 calories. The tablets used in the tests had the same composition as those used for the Beagle dogs and measured either 4 mm×4 mm or 6 mm×6 mm. The subjects were X-rayed at 30 minutes and at 1, 2, 4, 6, 8, 10, and approximately 12 hours after ingesting the tablets. In some subjects, visualization was achieved by ultrasound rather than X-rays.

Imaging revealed that in the fasted trials, the tablets left the stomach in 30 minutes to one hour after administration. In the fed trials, the tablets demonstrated multiple-hour retention in the stomach in all subjects, 80% of the contents of all tablets being retained at 4 hours. Five of the ten subjects retained the tablets for 6 hours or more, and four of these five retained them for ten hours or more.

EXAMPLE 10

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **9**. The formulation was as follows (all percentages are by weight): 48.5% metformin HCl; 49% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 9.66 mm diameter×6.95 mm height×19.24 mm length, and contained approximately 506 mg metformin HCl per tablet.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, additives, proportions, methods of formulation, and other parameters of the invention can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed is:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug within about eight hours after such immersion, and that remains substantially intact until all of said drug is released.

2. A dosage form of claim **1** in which the solubility of said drug in water is greater than one part by weight of said drug in five parts by weight of water.

3. A dosage form of claim **1** in which said drug is a member selected from the group consisting of metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, tramadol and ticlopidine hydrochloride.

4. A dosage form of claim **1** in which said drug is metformin hydrochloride.

5. A dosage form of claim **1** in which said drug is sertraline hydrochloride.

6. A dosage form of claim **1** in which said drug is captopril.

7. A dosage form of claim **1** in which said drug is vancomycin hydrochloride.

8. A dosage form of claim **1** in which said polymeric matrix is formed of a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

9. A dosage form of claim **8** in which said alkyl-substituted celluloses are members selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

10. A dosage form of claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

11. A dosage form of claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 4,500,000 to about 10,000,000.

12. A dosage form of claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 5,000,000 to about 8,000,000.

13. A dosage form of claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said drug one hour after such immersion.

14. A dosage form of claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said drug one hour after such immersion.

15. A dosage form of claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 80% of said drug one hour after such immersion.

16. A dosage form of claim **1** further comprising a member selected from the group consisting of glyceryl monostearate and sodium myristate, formulated with said drug to further retard the release of said drug to said gastric fluid.

17. A dosage form of claim **1** in which said polymeric matrix consists of two cylindrical tablets, each measuring about 9 mm to about 12 mm in length and about 6.5 mm to about 7 mm in diameter.

18. A dosage form of claim **1** in which said polymeric matrix consists of a single elongated tablet measuring about 18 mm to about 22 mm in length, about 6.5 mm to about 7.8 mm in width, and about 6.2 to 7.5 mm in height.

19. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach and doing so in a manner that substantially avoids the alteration of intestinal flora that said drug otherwise tends to cause, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

20. A method in accordance with claim **19** in which said drug is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, ceftazidine, and ciprofloxacin.

21. A method in accordance with claim **19** in which said drug is a highly soluble drug selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, and clindamycin.

22. A method of treating a subject suffering from infections selected from the group consisting of pneumonia, sinus bacterial infections, topical bacterial infections and staphylococcus infections, by administering to said subject a drug which is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, and ceftazidine, without substantially causing side effects resulting from the alteration of the intestinal flora of said subject, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

23. A method in accordance with claim **22** in which said drug is a highly soluble drug selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, and clindamycin.

24. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable by colonic bacterial enzymes residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal enzymes and said drug transporters.

25. A method in accordance with claim **24** in which said drug is a member selected from the group consisting of cyclosporine, digoxin, and doxifluridine.

26. A method in accordance with claim **24** in which said drug is doxifluridine.

27. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial degradation of said cyclosporine by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said cyclosporine dispersed therein at a weight ratio of cyclosporine to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid,

(d) releases substantially all of said cyclosporine within about ten hours after such immersion, and

(e) remains substantially intact until all of said cyclosporine is released,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding contact of said cyclosporine with said colonic bacterial enzymes.

28. A method of treating a subject for heart disease by administering digoxin to said subject without substantial degradation of said digoxin by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said digoxin while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said digoxin dispersed therein at a weight ratio of digoxin to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said digoxin one hour after such immersion in gastric fluid,

(d) releases substantially all of said digoxin within about ten hours after such immersion, and

(e) remains substantially intact until all of said digoxin is released,

thereby extending the release rate of said digoxin with time during said fed mode while releasing substantially all of said digoxin within said stomach and substantially avoiding contact of said digoxin with said colonic bacterial enzymes.

29. A method of treating a subject suffering from a condition selected from the group consisting of ovarian cancer, colorectal cancer, gastric cancer, renal cancer, and breast cancer, by administering doxifluridine to said subject without substantial degradation of said doxifluridine by intestinal enzymes or substantial inactivation of said doxifluridine by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said doxifluridine while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said doxifluridine dispersed therein at a weight ratio of doxifluridine to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said doxifluridine one hour after such immersion in gastric fluid,

(d) releases substantially all of said doxifluridine within about ten hours after such immersion, and

(e) remains substantially intact until all of said doxifluridine is released,

thereby extending the release rate of said doxifluridine with time during said fed mode while releasing substantially all of said doxifluridine within said stomach and substantially avoiding contact of said doxifluridine with said enzymes.

30. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also susceptible to inactivation by drug transporters residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said drug transporters.

31. A method in accordance with claim **30** in which said drug is a member selected from the group consisting of cyclosporine and paclitaxel.

32. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial inactivation of said cyclosporine by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said cyclosporine dispersed therein at a weight ratio of cyclosporine to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid,

(d) releases substantially all of said cyclosporine within about ten hours after such immersion, and

(e) remains substantially intact until all of said cyclosporine is released,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding inactivation of said cyclosporine by p-glycoprotein in said lower gastrointestinal tract.

33. A method of treating a subject suffering from cancer by administering paclitaxel to said subject without substantial inactivation of said paclitaxel by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said paclitaxel while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said paclitaxel dispersed therein at a weight ratio of paclitaxel to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said paclitaxel one hour after such immersion in gastric fluid,

(d) releases substantially all of said paclitaxel within about ten hours after such immersion, and

(e) remains substantially intact until all of said paclitaxel is released,

thereby extending the release rate of said paclitaxel with time during said fed mode while releasing substantially all of said paclitaxel within said stomach and substantially avoiding inactivation of said paclitaxel by p-glycoprotein in said lower gastrointestinal tract.

34. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach and whose bioavailability is substantially greater in an acidic

environment than an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

35. A method in accordance with claim **34** in which said drug is a member selected from the group consisting of esters of ampicillin, iron salts, digoxin, and ketoconazole.

36. A method in accordance with claim **34** in which said drug is a member selected from the group consisting of esters of ampicillin.

37. A method of treating a subject suffering from a bacterial infection by administering an ester of ampicillin to said subject while maintaining maximum bioavailability of said ester of ampicillin, said method comprising orally administering to said subject a dosage form of said ester of ampicillin while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said ester of ampicillin dispersed therein at a weight ratio of said ester of ampicillin to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ester of ampicillin one hour after such immersion in gastric fluid,

(d) releases substantially all of said ester of ampicillin within about ten hours after such immersion, and

(e) remains substantially intact until all of said ester of ampicillin is released,

thereby extending the release rate of said ester of ampicillin with time during said fed mode while releasing substantially all of said ester of ampicillin within said stomach and maintaining said ester of ampicillin in the acidic environment of said stomach during said release.

38. A method of treating a subject suffering from anemia by administering iron salts to said subject while maintaining maximum bioavailability of said iron salts, said method comprising orally administering to said subject a dosage form of said iron salts while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said iron salts dispersed therein at a weight ratio of iron salts to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said iron salts one hour after such immersion in gastric fluid,

(d) releases substantially all of said iron salts within about ten hours after such immersion, and

(e) remains substantially intact until all of said iron salts is released,

thereby extending the release rate of said iron salts with time during said fed mode while releasing substantially all of said iron salts within said stomach where said iron salts are maintained in an acidic environment.

39. A method of treating a subject suffering from a systemic fungal infection by administering ketoconazole to said subject while maintaining maximum bioavailability of said ketoconazole, said method comprising orally administering to said subject a dosage form of said ketoconazole while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said ketoconazole dispersed therein at a weight ratio of ketoconazole to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ketoconazole one hour after such immersion in gastric fluid,

(d) releases substantially all of said ketoconazole within about ten hours after such immersion, and

(e) remains substantially intact until all of said ketoconazole is released,

thereby extending the release rate of said ketoconazole with time during said fed mode while releasing substantially all of said ketoconazole within said stomach where said ketoconazole is maintained in an acidic environment.

40. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix in which said drug is dispersed at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

41. A method in accordance with claim **40** in which said drug is nelfinar mesylate.

42. A method of treating a subject infected with human immunodeficiency virus by administering nelfinar mesylate to said subject without substantial degradation of said nelfinar mesylate by intestinal flora or substantial inactivation of said nelfinar mesylate by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said nelfinar mesylate while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said nelfinar mesylate dispersed therein at a weight ratio of nelfinar mesylate to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said nelfinar mesylate into gastric fluid by the dissolving of said nelfinar mesylate by said gastric fluid and either erosion of said matrix or diffusion of said dissolved nelfinar mesylate out of said matrix,

(c) retains at least about 40% of said nelfinar mesylate one hour after such immersion in gastric fluid,

(d) releases substantially all of said nelfinar mesylate within about ten hours after such immersion, and

(e) remains substantially intact until all of said nelfinar mesylate is released,

thereby extending the release rate of said nelfinar mesylate with time during said fed mode while releasing substantially all of said nelfinar mesylate within said stomach where said nelfinar mesylate is maintained in an acidic environment.

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

44. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an acidic environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) protects any unreleased drug in said matrix from said gastric fluid,

(d) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(e) releases substantially all of said drug within about ten hours after such immersion, and

(f) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

45. A dosage form of claim **1** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises an alkyl-substituted cellulose.

46. A dosage form of claim **1** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

47. A dosage form of claim **1** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of from about 4,500,000 to about 10,000,000.

48. A method in accordance with claim **19** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

49. A method in accordance with claim **19** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of from about 4,500,000 to about 10,000,000.

50. A method in accordance with claim **19** in which said solid polymeric matrix comprises an alkyl-substituted cellulose.

51. A method in accordance with claim **19** in which said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

52. A method in accordance with claim **43** in which said drug is a member selected from the group consisting of metformin hydrochloride, lisinopril, captopril, buproprion, ganciclovir, and iron salts.

53. A method in accordance with claim **43** in which said drug is metformin hydrochloride.

54. A method in accordance with claim **43** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

55. A method in accordance with claim **43** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of from about 4,500,000 to about 10,000,000.

56. A method in accordance with claim **43** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

57. A method in accordance with claim **43** in which said solid polymeric matrix comprises an alkyl-substituted cellulose.

58. A method in accordance with claim **43** in which said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

59. A method in accordance with claim 43 in which said drug is metformin hydrochloride and said solid polymeric matrix comprises an alkyl-substituted cellulose.

60. A method in accordance with claim 43 in which said drug is metformin hydrochloride and said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

61. A dosage form of claim 1 in which said polymeric matrix is comprised of hydroxypropylmethylcellulose.

62. A dosage form of claim 1 in which said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

63. A dosage form of claim 1 in which said drug is metformin hydrochloride and said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

64. A dosage form of claim 1 in which said drug is metformin hydrochloride and said polymeric matrix is comprised of an alkyl-substituted cellulose.

65. A dosage form of claim 1 in which said drug is metformin hydrochloride and said polymeric matrix is comprised of hydroxypropylmethylcellulose.

66. A method in accordance with claim 43 in which said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

67. A method in accordance with claim 43 in which said drug is metformin hydrochloride and said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

68. A controlled-release oral drug dosage form for releasing metformin hydrochloride, said dosage form comprising a solid polymeric matrix with said metformin hydrochloride therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during the fed mode, that releases said metformin hydrochloride into gastric fluid by the dissolution and diffusion of said metformin hydrochloride out of said matrix by said gastric fluid, and that upon immersion in gastric fluid retains at least about 40% of said metformin hydrochloride one hour after such immersion.

69. The dosage form of claim 68, wherein said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthum gum.

70. The dosage form of claim 69, wherein said polymeric matrix comprises an alkyl-substituted cellulose.

71. The dosage form of claim 70, wherein said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

72. The dosage form of claim 71, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose.

73. The dosage form of claim 71, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose having a viscosity ranging from 11,000 to 110,000 centipoise as measured in a 2% solution at 20 C.

74. The dosage form of claim 68, wherein said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said metformin hydrochloride one hour after such immersion.

75. The dosage form of claim 68, wherein said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

76. The dosage form of claim 68, wherein said polymeric matrix comprises poly(ethylene oxide) having a molecular weight of at least about 4,000,000.

77. The dosage form of claim 68, wherein said polymeric matrix comprises poly(ethylene oxide) having a molecular weight ranging from about 4,500,000 to about 10,000,000.

78. The dosage form of claim 68, wherein said polymeric matrix comprises poly(ethylene oxide) having a molecular weight ranging from about 5,000,000 to about 8,000,000.

79. A controlled-release oral drug dosage form for releasing metformin hydrochloride, said dosage form comprising a solid polymeric matrix tablet with said metformin hydrochloride therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix tablet being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during the fed mode, that releases said metformin hydrochloride into gastric fluid by the dissolution and diffusion of said metformin hydrochloride out of said matrix by said gastric fluid, and that upon immersion in gastric fluid retains at least about 40% of said metformin hydrochloride one hour after such immersion.

80. The dosage form of claim 79, wherein said polymeric matrix of said polymeric matrix tablet comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthum gum.

81. The dosage form of claim 80, wherein said polymeric matrix comprises an alkyl-substituted cellulose.

82. The dosage form of claim 81, wherein said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

83. The dosage form of claim 82, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose.

84. The dosage form of claim 83, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose having a viscosity ranging from 11,000 to 110,000 centipoise as measured in a 2% solution at 20 C.

85. The dosage form of claim 79, wherein said polymeric matrix tablet upon immersion in gastric fluid retains at least about 50% of said metformin hydrochloride one hour after such immersion.

86. The dosage form of claim 79, wherein said polymeric matrix tablet upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

87. The dosage form of claim 79, wherein said polymeric matrix of said polymeric matrix tablet comprises poly (ethylene oxide) having a molecular weight of at least about 4,000,000.

88. The dosage form of claim 79, wherein said polymeric matrix of said polymeric matrix tablet comprises poly (ethylene oxide) having a molecular weight ranging from about 4,500,000 to about 10,000,000.

89. The dosage form of claim 79, wherein said polymeric matrix of said polymeric matrix tablet comprises poly (ethylene oxide) having a molecular weight ranging from about 5,000,000 to about 8,000,000.

* * * * *

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 13,793 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Office 2007 in Times New Roman 14 pt.

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/s/ Sasha Mayergoyz
Sasha Mayergoyz
JONES DAY
77 West Wacker
Chicago, IL 60601
(312) 269-1572
smayergoyz@jonesday.com

Counsel for Appellant Purdue Pharma L.P.

CERTIFICATE OF SERVICE

I hereby certify that on October 5, 2015, I served a copy of the foregoing on all counsel of record by CM/ECF.

/s/ Sasha Mayergoyz
Sasha Mayergoyz
JONES DAY
77 West Wacker
Chicago, IL 60601
(312) 269-1572
smayergoyz@jonesday.com

Counsel for Appellant Purdue Pharma L.P.